GLOBAL ORGANIZATION FOR EPA AND DHA OMEGA-3S

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April 27, 2018

RE: Request for Comments Dated 15 March 2018 on Proposed Draft NRV-NCD for EPA+DHA

Dear eWG Co-Chairs (Chile and Russian Federation):

The Global Organization for EPA and DHA Omega-3s (GOED) is an association of processors, refiners, manufacturers, distributors, marketers, retailers and supporters of products containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 fatty acids. GOED's membership represents a broad range of businesses, from small entrepreneurs to multinational food companies. The organization's objectives are to educate consumers about the health benefits of EPA/DHA and to collaborate with government groups, the healthcare community and the industry on issues related to omega-3s, while setting high standards for our business sector. As such, our members have a profound interest in ensuring that valuable information regarding EPA and DHA is communicated to consumers in a meaningful and timely way. Thus said, we appreciate the opportunity to provide feedback on the request for comments dated 15 March 2018.

Q1: Do you agree that NUGAG systematic reviews of RCT and prospective cohort studies present relevant convincing/generally accepted scientific evidence characterising the relationship between EPA and DHA and CHD mortality, as required by the first item of section 3.2.2 of the Annex to CAC/GL 2-1985?

No. GOED does not agree that the systematic reviews of RCTs and prospective cohort studies from the World Health Organization (WHO) Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health presents relevant convincing/generally accepted scientific evidence characterizing the relationship between EPA+DHA and Coronary Heart Disease (CHD) mortality, as required by the first item of section 3.2.2 (Selection of Nutrients and Appropriate Basis for NRVs-NCD) of the Annex to the *Guidelines on Nutrition Labelling* (CAC/GL2-1985).[1] In particular, NUGAG's methodology dramatically and artificially reduced evidence considered for CHD mortality in RCTs. This issue is specific to the NUGAG review of RCTs and not the review of prospective cohorts. The definition of CHD mortality is inconsistent between the two NUGAG reviews. GOED does believe, however, that ***the totality of available scientific evidence*** on the outcome of interest (i.e. CHD mortality/fatal CHD events) is convincing/generally accepted and supports the proposed draft NRV-NCD of 250 mg/day for EPA+DHA for inclusion in the

[1] http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FStandards%252FCAC%2BGL%2B2-1985%252FCXG_002e.pdf

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Guidelines on Nutrition Labelling (CAC/GL2-1985). GOED has compiled a list of global recommended intakes (see Appendix 1) for the eWG's reference.[2]

While NUGAG's evidence (see Table 1) clearly demonstrates an association between EPA+DHA intake and reduced risk of CHD mortality/fatal CHD events from observational trials (i.e. prospective cohorts) and confirms that the effect can be observed in RCTs for pre-planned subgroup analyses (e.g. coronary death), NUGAG downplayed the results because the RCT meta-analysis of the effect of EPA+DHA on CHD deaths did not reach statistical significance.

Table 1. NUGAG RCT vs Prospective Cohort Results

RCTs	**#Studies**	**N**	**RR**	**95% CI**
Meta-analysis of the effect of EPA+DHA on CHD deaths	21	73,491	0.93	0.79-1.09
Sensitivity analysis of the effect of EPA+DHA coronary death*	21	65,325	0.83	0.74-0.94
Prospective Cohort studies	**#Studies**	**N**	**RR**	**95% CI**
Fatal Coronary Heart Disease	9	5,904	0.81	0.68 to 0.97

*Omission of studies reporting only cardiac death

Among the potential reasons for CHD deaths not reaching statistical significance is that relevant fatal CHD events were missed in the NUGAG review of RCTs due to its definition of CHD mortality. While NUGAG adopts a prioritization scheme for CHD mortality variables in their review of RCTs, it does not employ the same methodology when reviewing observational evidence. Below is a comparison of the two definitions.

- CHD mortality (definition used in the report of RCTs):
  "We included data reported as coronary deaths, or where these were not reported, IHD death, fatal MI or cardiac death (using the first of these available in any study)."
- CHD mortality (definition used in the report of prospective cohort studies):
  "Fatal coronary heart disease: death from ischemic heart disease, including myocardial infarction, angina pectoris, or other forms of chronic ischemic heart disease."

According to a very recent consensus report on cardiovascular definitions for clinical trials, resulting from a nearly 10 year effort which included the U.S. Food and Drug Administration, when the specific cause of death is necessary to understand disease implications and therapeutic (or preventative) mechanisms, as it is in the present situation, the judgement of classification using

[2] While every recommendation may not be considered to be from an RASB, since the definition of RASB is still being debated, GOED has not removed any entries from the list.

uniform definitions is recommended.[3] Furthermore, there is acknowledgement that such classification is difficult because the classifications refer to both underlying cause and mode of death, with the potential for considerable overlap. Minimally, one would expect that the definition used for the NUGAG review of RCTs and review of prospective cohorts would have been the same. It is difficult to imagine that the totality of available scientific evidence regarding the relationship between EPA+DHA and CHD mortality is adequately interpreted when the RCT evidence is reviewed in one manner, and the observational evidence in another manner.

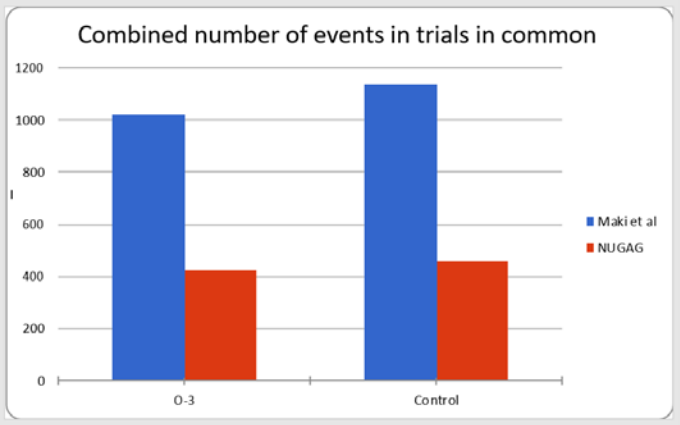
GOED believes the definition used by NUGAG (review of RCTs) artificially and dramatically reduced the number of events included in the analysis and thus decreased statistical power. To provide additional insight into the missed events, GOED refers to a publication reporting on a cardiac death meta-analysis[4] that was commissioned[5] in anticipation of the Codex work to establish an NRV-NCD for EPA+DHA. While this publication reports on a meta-analysis of supplemental EPA+DHA use and risk of cardiac death, as opposed to CHD death, it demonstrates consistent and statistically significant risk reductions of nearly 30% in up to 14 RCTs representing over 70,000 individuals. In addition, it corroborates NUGAG's findings and is part of the totality of available scientific evidence and should therefore be considered as part of the discussion to establish an NRV-NCD for EPA+DHA.

The NUGAG RCT and Maki et al. reviews included data from 21 and 20 studies, respectively, with 16 studies common between the two. Although pre-defined for both reviews, the events considered of relevance were not always the same between the reports of Maki et al. and NUGAG. Maki et al. included myocardial infarction (MI) (fatal), sudden cardiac death, sudden cardiac mortality, coronary mortality, cardiac mortality, or ischemic heart disease (IHD) mortality. NUGAG included data reported as coronary deaths, or where these were not reported, IHD death, fatal MI or cardiac death (using the first of these available in any study). For this reason, the authors in the respective reviews extracted a different number of mortality events for six of the 16 common studies in their analyses. The below graph shows that for the omega-3 and control groups, NUGAG reported 599 and 674 fewer events, respectively compared to Maki et al. Further details can be found in GOED's 17 November 2017 comments on the Report of the electronic Working Group (eWG) on Establishing an NRV-NCD for EPA and DHA (see Appendix 2).

[3] Hicks KA, Mahaffey KW, Mehran R, Nissen SE, Wiviott SD, Dunn B, Solomon SD, Marler JR, Teerlink JR, Farb A, Morrow DA, Targum SL, Sila CA, Hai MTT, Jaff MR, Joffe HV, Cutlip DE, Desai AS, Lewis EF, Gibson CM, Landray MJ, Lincoff AM, White CJ, Brooks SS, Rosenfield K, Domanski MJ, Lansky AJ, McMurray JJV, Tcheng JE, Steinhubl SR, Burton P, Mauri L, O'Connor CM, Pfeffer MA, Hung HMJ, Stockbridge NL, Chaitman BR, Temple RJ; Standardized Data Collection for Cardiovascular Trials Initiative (SCTI). 2017 Cardiovascular and Stroke Endpoint Definitions for Clinical Trials. Circulation. 2018; 137:961-972. http://circ.ahajournals.org/content/137/9/961.full.pdf?download=true

[4] Maki KC, Palacios OM, Bell M, Toth PP. Use of supplemental long-chain omega-3 fatty acids and risk for cardiac death: An updated meta-analysis and review of research gaps. J Clin Lipidol. Epub ahead of print 2017 Aug 2. http://www.lipidjournal.com/article/S1933-2874(17)30395-1/pdf

[5] GOED played no role in study design; in the collection, analysis, and interpretation of data; in the writing of the report; or in the decision to submit the article for publication.



Q2: Do you agree that for the purpose of establishing NRV-NCD for EPA/DHA opinions of RASBs that did not establish reference intake values for EPA/DHA should also be taken into consideration?

Yes. Scientific reviews from Recognized Authoritative Scientific Bodies (RASBs), regardless of whether they established reference intake values for EPA/DHA, should be discussed as part of the review process. The inclusion of such reviews represents a part of the totality of the scientific evidence and the omission of such reviews introduces bias into the evaluation process.

Q3: Do you agree that a change may be required in the text of the second paragraph of Section 3.1 of the Annex in CAC/GL 2-1985 to account for opinions of RASBs that did not establish reference intake values for EPA/DHA?

Yes. GOED supports a review of the totality of the available scientific evidence and the omission of opinions of RASBs who did not establish reference intake values introduces bias into the process. Thus said, should consideration of reviews from RASBs in which a reference intake value was not established require a change to the text of the second paragraph of section 3.1 of the Annex in CAC/GL 2-1985, then GOED supports such change.

Q4: Do you agree that the criteria convincing, probable, possible and insufficient should no longer be used in describing the level of scientific evidence required for establishing the NRV-NCD for EPA/DHA?

No. The use of the criteria convincing, probable, possible and insufficient are acceptable for use, but the use of only GRADE-based descriptions is too restrictive in that it may eliminates the ability to consider reviews from other RASBs, who contribute to the totality of the available scientific evidence.

While GRADE provides a way to evaluate the strength of evidence for each type of study, it does not provide a good way to combine these assessments. In addition, GRADE ignores all other

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evidence, including the effect on biomarkers or plausible mechanistic explanations. The strength of GRADE over other systems is that it separates the strength of evidence from the strength of recommendation, and leaves these decisions to different groups of people, with different expertise. Focusing on only strength of evidence misses the point, and leaves the recommendations in the hands of data analysts instead of the public health experts and risk assessors, who are the ones with the necessary expertise to evaluate the balance between risks and benefits of any given intervention.

Q5: Do you agree that a level of evidence quality under the GRADE classification accepted for the purpose of establishing the NRV-NCD for EPA/DHA should be specified?

No. By specifying a level of evidence quality under the GRADE classification, you effectively eliminate the ability to consider reviews that are not based on GRADE. The totality of the available scientific evidence needs to be considered.

Q6: Do you agree that a new revision of the first item of Section 3.2.2 of the Annex to CAC/GL 2-1985 may need to be agreed to facilitate further discussion of the NRV-NCD for EPA/DHA?

No. The first item of Section 3.2.2 of the Annex to CAC/GL 2-1985 acknowledges and accommodates a range of evidence grading methodologies by accepting “relevant convincing”, “generally accepted”, “or a comparable level of evidence under the GRADE classification”. Without accommodation of a variety of generally accepted evidence grading terminology, only evidence evaluated using GRADE will ever enter deliberations. Given that GRADE has not been globally adopted by all relevant RASBs and does not reflect all elements of a cause and effect relationship, the restriction to only GRADE-based evaluations effectively eliminates consideration of any other RASB relevant evidence review and curtails an evaluation of the totality of the available scientific evidence.

To conclude, GOED would like to emphasize its appreciation of the opportunity to provide feedback on the request for comments. We look forward to a constructive discussion on this topic at the November Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) meeting in Berlin, Germany.

Sincerely,

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Vice-President, Regulatory & Scientific Affairs

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Appendix 1

Global Recommendations for EPA and DHA Intake (Rev 26 April 2018)

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
Global	World Health Organization (WHO)/Food and Agriculture Organization of the United Nations (FAO)[1]	Authoritative Body	General adult population	▪ n-3 PUFAs: 1-2% of energy/day	2003
	Food and Agriculture Organization of the United Nations (FAO)[2]	Authoritative Body	0-6 months	▪ DHA: 0.1-0.18%E	2008
			6-24 months	▪ DHA: 10-12 mg/kg bw	
			2-4 years	▪ EPA + DHA: 100-150 mg	
			4-6 years	▪ EPA + DHA: 150-200 mg	
			6-10 years	▪ EPA + DHA: 200-250 mg	
			Adults as part of healthy diet	▪ 0.250-2.0 g	
			Pregnant/Lactating Women	▪ EPA + DHA: 0.3 g/d of which DHA should be at least 0.2 g/d	
	International Society for the Study of Fatty Acids and Lipids (ISSFAL)	Expert Scientific Organization	General adult population for cardiovascular health[3]	▪ at least 500 mg/day of EPA+DHA	2004
			Pregnant/Lactating Women[4]	▪ DHA: 200 mg/day	2007
	NATO Workshop on ω-3 and ω-6 Fatty Acids[5]	Workshop	General Adult Population	▪ 300-400 mg EPA+DHA/day	1989
	World Association of Perinatal Medicine[6]	Working Group	Pregnant and Lactating Women	▪ 200 mg DHA/ day	2008
			Infants, when breastfeeding is not possible	▪ 0.2-0.5% wt total fat	
	World Gastroenterology Organisation[7]	Expert Scientific Organization	General Adult Population	▪ 3-5 servings/wk of fish	2008

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
Australia	National Heart Foundation of Australia[8]	Expert Scientific Organization	Primary prevention of coronary heart disease	2–3 servings of fish (including oily fish) per week which provides about 250–500 milligrams of marine-sourced omega-3s, EPA and DHA, per day	2015
			People with existing heart disease	2–3 servings of fish and seafood as part of a heart-healthy diet	
	Australian & New Zealand Health Authorities (Department of Health & Ageing, National Health & Medical Research Council)[9]	Authoritative Bodies	Infants (0-12 mo)	▪ 0.5 g n-3 polyunsaturated fats/day adequate intake	2006
			Boys & Girls (1-3 yrs)	▪ 40 mg total LC n-3 (DHA+EPA+DPA) / day adequate intake	
			Boys & Girls (4-8 yrs)	▪ 55 mg total LC n-3 (DHA+EPA+DPA) / day adequate intake	
			Boys & Girls (9-13 yrs)	▪ 70 mg total LC n-3 (DHA+EPA+DPA) / day adequate intake	
			Boys (14-18 yrs)	▪ 125 mg total LC n-3 (DHA+EPA+DPA) / day adequate intake	
			Girls (14-18 yrs)	▪ 85 mg total LC n-3 (DHA+EPA+DPA) / day adequate intake	
			Men (19+ yrs)	▪ 160 mg total LC n-3 (DHA+EPA+DPA) per day adequate intake	
			Women (19+ yrs)	▪ 90 mg total LC n-3 (DHA+EPA+DPA) / day adequate intake	
			Pregnancy (14 -18 yrs)	▪ 110 mg total LC n-3	

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				(DHA+EPA+DPA) / day	
			Pregnancy (19-50 yrs)	▪ 115 mg total LC n-3 (DHA+EPA+DPA) / day	
			Lactating (14-18 yrs)	▪ 140 mg LC n-3 (DHA+EPA+DPA) / day	
			Lactating (19-50 yrs)	▪ 145 mg LC n-3 (DHA+EPA+DPA) / day	
			Men-Suggested dietary target to reduce chronic disease risk	▪ 610mg LC n-3 (DHA+EPA+DPA) / day	
			Women-Suggested dietary target to reduce chronic disease risk	▪ 430mg LC n-3 (DHA+EPA+DPA) / day	
	Defence Science and Technology Organisation, Australian Government Department of Defence[10]	Authoritative Body	Male soldiers	▪ 610mg EPA+DPA+DHA/ day	2009
			Female soldiers	▪ 430mg EPA+DPA+DHA / day	
	Australasian Society of Clinical Immunology and Allergy Limited (ASCIA)[72]	Expert Scientific Organization	Pregnant and lactating women	▪ Up to 3 serves of oily fish per week may be beneficial, as there is some evidence that omega-3 fatty acids (found in oily fish) during pregnancy and breastfeeding may help prevent eczema in early life.	2016
Europe	Expert Workshop of the European Academy of Nutritional Sciences[11]	Expert Scientific Organization	General Adult Population	▪ People who do not eat fish should consider obtaining 200 mg EPA + DHA from other sources	1998
	European Food Safety Authority[12]	Authoritative Body	General Adult Population	▪ 250mg EPA+DHA /day	2010

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
			Pregnant & Lactating Women	▪ 100-200 mg DHA / day in addition to general adult requirements	
			Children 7-24 months	▪ 100 mg DHA / day	
			Children 2-18 years	▪ 250mg EPA+DHA /day	
	The PeriLip and EARNEST projects of the European Commission[4]	Expert Scientific Organization	Pregnant & Lactating Women	▪ 200mg DHA/day	2007
	The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts)[13]	Expert Scientific Organization	General Adult Population for Cardiovascular Disease Risk Reduction	▪ Eat fish 1-2 times per week, one of which to be oily fish.	2016
	Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology[14]	Expert Scientific Organization		• Increase consumption of omega-3 fatty acid (oily fish) • Supplementation with 1 g of fish oil in patients with a low intake of oily fish ▪ omega-3 supplements should be considered in patients who do not tolerate statins, especially if TG >150 mg/dL (1.7 mmol/L)	2008
	Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS)[15]	Expert Scientific Organization	General Adult Population for Cardiovascular Disease Risk Reduction	▪ At least two or three portions of fish per week	2011
			Secondary prevention of CVD	▪ 1 g/day n-3 unsaturated fats, which is not easy to	

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				derive exclusively from natural food sources, and use of nutraceutical and/or pharmacological supplements may be considered	
	The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC[64]	Expert Scientific Organization	patients with symptomatic (NYHA class II–IV) systolic heart failure	An n-3 PUFA preparation may be considered to reduce the risk of death and the risk of cardiovascular hospitalization in patients treated with an ACE inhibitor (or ARB), beta-blocker, and an MRA (or ARB)	2012
	The European Society for Clinical Nutrition and Metabolism (ESPEN)[73]	Expert Scientific Organization	surgical and non-surgical ICU patients	▪ supports the use of fish oil in nutrition support in surgical and non-surgical ICU patients	2014
France	AFFSA[16]	Authoritative Body	General Adult Population	▪ 500 mg EPA + DHA / day ▪ 250 mg EPA / day ▪ 250 mg DHA / day	2010
			Metabolic Syndrome-Diabetes-Obesity Risk Reduction	▪ 500 mg EPA + DHA / day	
			Cardiovascular Risk Reduction	▪ 500-750 mg EPA + DHA / day	
			Breast & Colon Cancer Risk Reduction	▪ 500 mg EPA + DHA / day	
			Neuropsychiatric Risk Reduction	▪ >200-300 mg EPA + DHA / day	
			Age-Related Macular Degeneration Risk Reduction	▪ 500 mg EPA + DHA / day	
			Infants (0-6 months)	▪ 0.32% of fats from DHA	

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				▪ EPA < DHA	
			Infants & Toddlers (6 months to 3 years)	▪ 70mg DHA /day	
			Children (3-9 years)	▪ 125mg DHA /day ▪ 250mg EPA+DHA /day	
			Adolescents (9 to 18 years)	▪ 250mg DHA /day ▪ 250mg EPA+DHA /day	
			Pregnant & Lactating Women	▪ 250mg DHA /day ▪ 250mg EPA+DHA day	
	ANSES[77]	Authoritative Body	Adult men and women	▪ 250 mg/day DHA ▪ 250 mg/day EPA	2016
Austria	Austrian Society for Nutrition (as part of joint effort with Germany and Switzerland)[17]	Expert Scientific Organization	General adult population	▪ 250mg LCPUFA / day for primary prevention of CVD	2008
			General adult population	▪ 0.5% of energy total n-3 PUFA intake	
			CHD Patients	▪ 1g LCPUFA / day for secondary prevention of CVD	
			Pregnant & nursing women	▪ At least 200mg DHA / day	
Germany	German Society for Nutrition[69]	Expert Scientific Organization	Vegan adult population	▪ No specific recommendation, but classified EPA and DHA as "potentially critical nutrients" for strict vegans. Critical nutrients should be added – either in dietary supplements or fortified foods to achieve recommended 250 mg/day EPA+DHA.	2016
	German Society for Nutrition[67]	Expert	General adult population	▪ 250 mg/day EPA+DHA for	2015

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
		Scientific Organization		primary prevention of CHD	
	German Society for Nutrition (as part of joint effort with Austria and Switzerland)[17]	Expert Scientific Organization	General adult population	▪ 250mg LCPUFA / day for primary prevention of CVD	2008
			General adult population	▪ 0.5% of energy total n-3 PUFA intake	
			CHD Patients	▪ 1g LCPUFA / day for secondary prevention of CVD	
			Pregnant & nursing women	▪ At least 200mg DHA / day	
	Healthy Start - Young Family Network[25, 45, 57]	Expert Scientific Organization	Pregnant women	• to supply the recommended 200mg/day of DHA, consume 2 servings/wk of marine fish, including at least one serving of fatty sea fish (such as mackerel, Herring, sardines, salmon) ▪ pregnant women who do not regularly consume fish, the use of supplements with the Omega-3 fatty acid DHA is recommended	2012-2013
Italy	Multiple (see publication)[70]	Multiple	Pregnant Women	▪ An adequate intake of DHA, essential for the growth and development of brain and retina, is of utmost importance	2016
	Italian Society of Human Nutrition[71]	Expert	Children 2 years and	▪ at least 250 mg/day in	2014

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
		Scientific Organization	older	the form of EPA+DHA	
			Children less than 2 years old	▪ for neurological and cognitive development, 100 mg/day of DHA, in addition to 250 mg/day of EPA+DHA	
	Ministry of Health, Department of Prevention and Communication General, General Administration of Veterinary Health and Food[76]	Authoritative Body	elderly	▪ In the absence of eating fish at least 3X/week, obtain omega-3s through supplementation	unknown
Switzerland	Swiss Society for Nutrition Research / Swiss Nutrition Association (as part of joint effort with Austria and Germany)[17]	Expert Scientific Organization	General adult population	▪ 250mg LCPUFA / day for primary prevention of CVD	2008
			General adult population	▪ 0.5% of energy total n-3 PUFA intake	
			CHD Patients	▪ 1g LCPUFA / day for secondary prevention of CVD	
			Pregnant & nursing women	▪ At least 200mg DHA / day	
Poland	Polish Gynecological Society[60]	Scientific Organization	Pregnant Women	▪ pregnant women at low risk of preterm birth should take at least 600 mg/day DHA ▪ pregnant women at high risk of preterm birth should take at least 1000 mg/day DHA	2014
Belgium	Superior Health Council of Belgium[18]	Authoritative Body	7-12 months	▪ 100 mg/day DHA	2016
			1-3 years	▪ 100 mg/day DHA	
			>3 years	▪ 250-500 mg/day EPA+DHA	

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
			Adults	▪ 250-500 mg/day EPA+DHA	
Netherlands	Health Council of the Netherlands	Authoritative Body	0-5 months[19]	▪ DHA: 20 mg/kg/day	2001
			6-11 months[19]	▪ N-3 fatty acids from fish: 15-20 mg/kg/day	
			1-18 years old[19]	▪ N-3 fatty acids from fish: 15-20 mg/kg/day	
			19 years +[19]	▪ N-3 fatty acids from fish: 20 mg/kg/day	
			Pregnant women[19]	▪ N-3 fatty acids from fish: 20 mg/kg/day	
			Lactating women[19]	▪ N-3 fatty acids form fish: 20 mg/kg/day	
			Adults[20]	• Eat one serving of fish weekly, preferably oily fish	2015
Scandinavia	Nordic Council of Ministers[21]	Authoritative Body	6-11 months	▪ n-3 fatty acids should contribute at least 1 E%	2013
			12-23 months	▪ n-3 fatty acids should contribute at least 0.5 E%	
			Adults and children from 2 yrs of age	▪ n-3 fatty acids should contribute at least 1.0 E%	
			Pregnant & Lactating Women	▪ 1 E% from n-3 fatty acids of which 200 mg/d should be DHA	
Turkey	Dietary Guidelines for Turkey[78]	Authoritative Body	Males and females 2+ years	▪ 250 mg/day EPA+DHA	2016
			Pregnant and lactating women	▪ 250 mg/day EPA+DHA plus 100-200 mg DHA	
United Kingdom	British Nutrition Foundation[22]	Expert Scientific Organization	Adults, 19-50 yrs	▪ one to two portions of oil-rich fish per week, which will provide around 2-3g of the very long	1999

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				chain *n-3* fatty acids ▪ weekly intake of 1.5g of EPA + DHA	
	Committee on Medical Aspects of Food Policy (COMA)[23]	Authoritative Body	Adults	▪ at least two portions of fish, of which one should be oily, weekly ▪ n-3 PUFA intake: 0.2 g/day	1994
	Scientific Advisory Committee on Nutrition (SACN)[24]	Authoritative Body	Adults	▪ at least two portions of fish, of which one should be oily, weekly ▪ n-3 PUFA intake: 0.45 g/day	2004
	National Institute for Health and Clinical Excellence (May 2008)[26]	Authoritative Body	People at high risk of or with CVD	▪ consume at least two portions of fish per week, including a portion of oily fish	2008
	Joint British Societies[27]	Expert Scientific Organization	General Adult Population	▪ Regular intake of fish and other sources of omega 3 fatty acids (at least two servings of fish per week)	2005
	Irish Heart Foundation[54]	Expert Scientific Organization	General Adult Population	▪ 200 mg/day long-chain fatty acids	
	British Dietetic Association[66]	Expert Scientific Organization	General Population	▪ Two Portions per week of fish, one of which should be oily; equals ~450mg EPA+DHA	2014
	National Collaborating Center for Primary Care[28]	Expert Scientific Organization	General Adult Population	▪ At least two servings of omega-3 fatty acid containing fish per week	2007
			People with Established CVD	▪ At least two servings of omega-3 fatty acid	

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				containing fish per week week)	
Spain	Spanish Society of Intensive Care Medicine and Coronary Units and Spanish Society of Parenteral and Enteral Nutrition[29]	Expert Scientific Organization	Individuals with acute coronary syndrome and patients with chronic heart failure	▪ Administration of 1 g/day of omega-3 (EPA+DHA) in the form of fish oil can prevent sudden death in the treatment of acute coronary syndrome and can also help to reduce hospital admission for cardiovascular events in patients with chronic heart failure	2011
	Spanish Society of Intensive Care Medicine and Coronary Units and Spanish Society of Parenteral and Enteral Nutrition[30]	Expert Scientific Organization	patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS)	▪ An enteral diet enriched with ω-3 diet fatty acids may have a beneficial effects	2011
	Spanish Menopause Society[75]	Expert Scientific Organization	Postmenopausal women	▪ 250 mg/day EPA+DHA	2017
Russia	Customs Union Commission[61]	Authoritative Body	Adults	▪ EPA 600 mg ▪ DHA 700 mg	2010
Brazil	Brazilian Society of Cardiology[31]	Expert Scientific Organization	Patients with coronary artery disease	▪ supplementation of 1 g / day of omega-3 (EPA + DHA) capsules	2007
	Brazilian Society of Cardiology[74]	Expert Scientific Organization	Adults for primary and secondary risk prevention	▪ Consumption ≥ 2 servings/week of fish rich in EPA and DHA	2017
			Adults for cardiovascular risk prevention	▪ EPA and DHA supplements (no specified amount	
			Adults with severe	▪ Supplementation with	

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
			hypertriglyceridemia (>500 mg/dL) with risk of pancreatitis refractory to nonpharmacological measures and drug treatments	EPA and DHA (2-4 g)	
			Individuals with mild to moderate hypertriglyceridaemia	▪ Supplementation with EPA and DHA (1-5 g/day)	
			Individuals with heart failure	▪ Supplementation with EPA and DHA (1 g /day)	
	Brazilian Association of Nutrition (ABRAN)[65]	Expert Scientific Organization	Women who are pregnant or lactating	▪ 200 mg/day DHA	2014
			Infants < 6 months	0.2 to 0.5% of total lipids as DHA	2014
United States	National Lipid Association[68]	Expert Scientific Organization	General	Therapeutic dosages of EPA + DHA for TG reduction are 2.0 to 4.0 g/day. Strength of Evidence = B; Quality of Evidence = Moderate	2015
United States	National Lipid Association[68]	Expert Scientific Organization	General	For primary and secondary prevention of atherosclerotic cardiovascular disease (ASCVD), consuming ≥2 servings/week of fish/seafood (preferably oily) is recommended. One serving is equal to 3.5 to 4 oz. and should ideally not be prepared using deep-frying. Strength of Evidence = A; Quality of Evidence = Moderate	2015

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
United States	National Lipid Association[68]	Expert Scientific Organization	General	For patients with known ASCVD, suggestive, but not conclusive, evidence from RCTs is available for a benefit of long-chain omega-3 fatty acid supplementation at ~1 g/day EPA + DHA on cardiac mortality, but not non-fatal ASCVD events. EPA + DHA supplements may be considered for such patients, especially those who do not consume the recommended intakes of EPA + DHA from dietary sources. Strength of Evidence = C; Quality of Evidence = Low	2015
United States	National Lipid Association[68]	Expert Scientific Organization	General	For patients with heart failure, 1 g/day of EPA + DHA is recommended as an adjunct to heart failure therapy. Strength of Evidence = A; Quality of Evidence = Moderate	2015
United States	National Lipid Association[68]	Expert Scientific Organization	Women	Non-statin drug therapy with cholesterol absorption inhibitor, bile acid sequestrant, fibric acid, nicotinic acid, or long-chain omega-3 fatty acid concentrates (the latter currently indicated only for very high TG) may be	2015

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				considered for women with contraindications for, or intolerance to, statin therapy, or in combination with statin therapy for patients who need additional lowering of atherogenic cholesterol to achieve treatment goals. Strength of Evidence = A; Quality of Evidence = High	
United States	National Lipid Association[68]	Expert Scientific Organization	Pregnant and Nursing Women	Very high TG (≥500 mg/dL) may be treated during pregnancy with diet/lifestyle management plus prescription omega-3 fatty acids; fenofibrate or gemfibrozil may be administered beginning early in the second trimester, based on clinical judgment. These agents may be used during breast feeding. Strength of Evidence = B; Quality of Evidence = Low	2015
United States	National Lipid Association[68]	Expert Scientific Organization	HIV Infected Persons	Elevated TG ≥500 mg/dL that is refractory to lifestyle modification or changes in ART (if an option) should generally be treated with either a fibrate (fenofibrate preferred) or prescription omega-3 fatty acids. After TG is lowered (<500 mg/dL),	2015

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				non-HDL-C and LDL-C should be reassessed for appropriate management. Strength of Evidence = B; Quality of Evidence = Moderate	
United States	National Lipid Association[68]	Expert Scientific Organization	Patients with Residual Risk Despite Statin and Lifestyle Therapy	Fibrates and prescription omega-3 fatty acids are first-line drug choices for patients with TG ≥500 mg/dL, although consideration may be given to using statin therapy as a first-line drug in patients with TG 500-999 without a history of pancreatitis. Strength of Evidence = E; Quality of Evidence = Moderate	2015
United States	National Lipid Association[68]	Expert Scientific Organization	Patients with Residual Risk Despite Statin and Lifestyle Therapy	In patients with elevated TG (200 to 499 mg/dL) on maximum tolerated statin therapy who are at their LDL-C goal but not their non–HDL-C goal, the addition of therapies that primarily lower TG and VLDL-C (fibrates, high-dose omega-3 fatty acids) may be considered to help achieve atherogenic cholesterol goals. Subgroup analyses from cardiovascular outcomes studies provide suggestive evidence of reduced ASCVD event risk	2015

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				with the addition of a TG-lowering agent to statin therapy, particularly in patients with the combination of elevated TG and low HDL-C. Strength of Evidence = B; Quality of Evidence = Moderate	
United States	Institute of Medicine[32]	Authoritative Body	Boys & Girls 1-3 yrs	▪ ALA: 0.7 g/day of which ~ 10% EPA+DHA	2005
			Boys & Girls 4-8 yrs	▪ ALA: 0.9 g/day of which ~ 10% EPA+DHA	
			Boys 9-13 yrs	▪ ALA: 1.2 g/day of which ~ 10% EPA+DHA	
			Boys 14-18 yrs	▪ ALA: 1.6 g/day of which ~ 10% EPA+DHA	
			Girls 9-13 yrs	▪ ALA: 1.0 g/day of which ~ 10% EPA+DHA	
			Girls 14-18 yrs	▪ ALA: 1.1 g/day of which ~ 10% EPA+DHA	
			Adult men ≥ 19 yrs	▪ ALA: 1.6 g/day of which ~ 10% EPA+DHA	
			Adult women ≥ 19 yrs	▪ ALA: 1.1 g/day of which ~ 10% EPA+DHA	
	American Diabetes Association[55]	Expert Scientific Organization	Individuals with diabetes	Eat fish (particularly fatty fish) at least two times (two servings) per week.	2013
	Academy of Nutrition and Dietetics (formerly American Dietetics Association)	Expert Scientific Organization	General Adult Population[56]	▪ 500 mg EPA+DHA per day	2014
			Varied[53]	Those with increased requirements (e.g., pregnant and lactating women or those with diseases associated with	2003

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				poor essential fatty acid status) or those at risk for poor conversion (e.g., people with diabetes) may benefit from direct sources of long-chain n-3 fatty acids, such as DHA-rich microalgae	
	March of Dimes[34]	Expert Scientific Organization	Pregnant and Nursing Women	▪ 200 mg DHA/day	2009
	Omega-3 Fatty Acids Subcommittee, assembled by the Committee on Research on Psychiatric Treatments of the American Psychiatric Association (APA)[36]	Expert Scientific Organization	Adults	▪ Eat fish >/= 2X/wk	2006
			Patients with mood, impulse control, or psychotic disorders	▪ 1 g EPA + DHA / day	
	American Heart Association	Expert Scientific Organization	Secondary prevention of CHD and sudden cardiac death among patients with prevalent CHD[37]	▪ unspecified	2017
			Secondary prevention of outcomes in patients with heart failure[37]	▪ unspecified	2017
			General adult population[58]	▪ Fish with 500 mg or more of EPA+DHA per 85 g (3 oz cooked) can apply for the AHA Heart-Check food certification program at heartcheckmark.org.	unknown
			Patients with high triglycerides[51]	• …increasing consumption of marine-based omega-3 products,…, will further	2011

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				optimize triglyceride-lowering efforts.	
			Cardiovascular Disease Risk Reduction in Women[38]	▪ Consume fish, especially oily fish, at least twice a week ▪ Consumption of omega-3 fatty acids in the form of fish or in capsule form may be considered in women with hypercholesterolemia and/or hypertriglyceridemia for primary and secondary prevention	2011
			Patients with Coronary and Other Atherosclerotic Vascular Disease[39]	• For all patients, it may be reasonable to recommend omega-3 fatty acids from fish or fish oil capsules (1 g/d) for CVD risk reduction	2011
	U.S. Dept of Agriculture and U.S. Department of Health and Human Services[40]	Authoritative Body	General adult population	▪ Consumption of about eight ounces per week of a variety of seafood, which provide an average consumption of 250 mg per day of EPA and DHA, is associated with reduced cardiac deaths among individuals with and without preexisting CVD	2016

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
			Pregnant or breastfeeding women	▪ consumption by women who are pregnant or breastfeeding of at least eight ounces per week from seafood choices that are sources of DHA is associated with improved infant health outcomes	
	Executive Office of the President[50]	Authoritative Body	General population	• Dietary Guidelines and Food Guide Pyramid should be revised to emphasize the benefits of…increasing consumption of foods rich in omega-3 fatty acids	2003
	Agency for Healthcare Research and Quality[49]	Authoritative Body	General population	• Fish and fish oil supplements reduce the risk of cardiovascular disease	2004
	American Academy of Pediatrics[41]	Expert Scientific	Nursing Women	• The mother's diet should	2012

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
		Organization		include an average daily intake of 200 to 300 mg of the ω-3 long-chain PUFAs (DHA) to guarantee a sufficient concentration of preformed DHA in the milk. Consumption of 1 to 2 portions of fish (e.g., herring, canned light tuna, salmon) per week will meet this need. The concern regarding the possible risk from intake of excessive mercury or other contaminants is offset by the neurobehavioral benefits of an adequate DHA intake and can be minimized by avoiding the intake of predatory fish (e.g., pike, marlin, mackerel, tile fish, swordfish). Poorly nourished mothers or those on selective vegan diets may require a supplement of DHA as well as multivitamins	
Canada	Minister of National Health and	Authoritative	General adult population	• 1.2-1.6 g/day total n-3	1990

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
	Welfare, Canada[42]	Body		PUFAs (ALA, EPA, DHA)	
	Dietitians of Canada[33]	Expert Scientific Organization	General adult population	• 500 mg n-3 long-chain PUFAs/day	2007
India	Cardiology Society of India[59]	Expert Scientific Organization	For patients with high triglycerides and patients after MI for secondary prevention	• Omega-3 acid ethyl esters (2-4g/day)	2012
China	Chinese Nutrition Society[62]	Expert Scientific Organization	0 up to 4 years	• 100 mg/day DHA	2014
			18+ years	• 250 – 2000 mg /day EPA+DHA	
			Pregnant & lactating women	• 250 mg/day EPA+DHA of which 200 mg should be DHA	
Japan	Ministry of Health, Labour and Welfare[43]	Authoritative Body	0-5 months – boys and girls	• 0.9g total omega-3 per day	2014
			6-11 months- boys and girls	• 0.8g total omega-3 per day	
			1-2 years – Boys	• 0.7g total omega-3 per day	
			1-2 years – Girls	• 0.8g total omega-3 per day	
			3-5 years – Boys	• 1.3g total omega-3 per day	
			3-5 years – Girls	• 1.1g total omega-3 per day	
			6-7 years – Boys	• 1.4 total omega-3 per day	
			6-7 years –Girls	• 1.3g total omega-3 per day	
			8-9 years – Boys	• 1.7g total omega-3 per day	
			8-9 years – Girls	• 1.4g total omega-3 per	

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				day	
			10-11 years – Boys	• 1.7g total omega-3 per day	
			10-11 years – Girls	• 1.5g total omega-3 per day	
			12-14 years – Boys	• 2.1g total omega-3 per day	
			12-14 years – Girls	• 1.8g total omega-3 per day	
			15-17 years – Boys	• 2.3g total omega-3 per day	
			15-17 years – Girls	• 1.7g total omega-3 per day	
			Adults (18-29 years) – Men	• 2.0g total omega-3 per day	
			18-29 years – Women	• 1.6g total omega-3 per day	
			30-49 years – Men	• 2.1g total omega-3 per day	
			30-49 years – Women	• 1.6g total omega-3 per day	
			50-69 years – Men	• 2.4g total omega-3 per day	
			50-69 years – Women	• 2.0g total omega-3 per day	
			Over 70 years – Men	• 2.2g total omega-3 per day	
			Over 70 years – Women	• 1.9g total omega-3 per day	
			Pregnant & Lactating Women	• 1.8g total omega-3 per day	
Malaysia	Ministry of Health	Authoritative	Acute ST Segment	• Increase intake of omega	2014 (3rd edition)

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
		Body	Elevation Myocardial Infarction[46]	3-fatty acids by eating fish at least twice a week.	
			Women with CHD[47]	• omega-3-fatty-acids (>1gm/day) have been found to be beneficial	2007
			Management of Dyslipidemia[48]	• A dose of 3-9 gm/day to lower TG levels • A dose of 0.75-1 gm/day as secondary prevention to prevent sudden death	2011
			For people with high risk or secondary prevention	• 1000 mg EPA + DHA/day as supplement for people who don't eat fish	2011
Singapore	Health Promotion Board[63]	Authoritative Body	General population	• 2 servings/week fish	2014
Taiwan	Taiwan Society of Lipids and Atherosclerosis[79]	Expert Scientific Organization	Individuals with very high triglycerides (>500 mg/dL)	• Omega-3 fatty acids (dose unspecified)	2017
			patients with coronary heart disease and hypertriglyceridemia	• EPA and DHA (dose unspecified)	
Thailand	Food and Drug Authority	Authoritative Body	General Population	• EPA+DHA NMT 1000 mg/day	Unknown – no reference located
Israel	Israel Heart Society[44]	Expert Scientific Organization	For the general public or primary prevention	• 500-1000 mg EPA + DHA/day as fish	2011

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Appendix 2

GLOBAL ORGANIZATION FOR EPA AND DHA OMEGA-3S

Submitted via email ccnfsdu@bmel.bund.de codex@fao.org

TO: German Secretariat of CCNFSDU

FROM: Global Organization for EPA and DHA Omega-3s (GOED)

RE: Agenda Item 6 - Proposed Draft NRV-NCD for EPA and DHA long chain omega-3 fatty acids

DATE: November 17, 2017

The Global Organization for EPA and DHA Omega-3s (GOED) is an association of processors, refiners, manufacturers, distributors, marketers, retailers and supporters of products containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) omega-3 fatty acids. GOED's membership represents a broad range of businesses, from small entrepreneurs to multinational food companies. The Organization's objectives are to educate consumers about the health benefits of EPA and DHA and to collaborate with government groups, the healthcare community and the industry on issues related to omega-3s, while setting high standards for our business sector.

GOED would like to provide the following comments on the Report of the electronic Working Group (eWG) on Establishing an NRV-NCD for EPA and DHA, Codex document CX/NFSDU 17/39/6, in relation to Agenda item 6 - Proposed Draft NRV-NCD for EPA and DHA long chain omega-3 fatty acids, for discussion at the 39th Session of the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) to be held in Berlin, Germany from 4-8 December 2017. GOED kindly requests our following comments be circulated to Codex members and observers and/or uploaded to the Codex website as a conference room document (CRD).

GENERAL COMMENTS

After a thorough review of the abridged systematic reviews from the World Health Organization (WHO) Nutrition Guidance Expert Advisory Group Subgroup on Diet and Health (hereafter 'NUGAG'), as well as a wealth of other data presented below, GOED concludes that the totality of the available scientific evidence on the outcome of interest (i.e. Coronary Heart Disease (CHD) mortality/fatal CHD events) is convincing/generally accepted and supports the proposed draft NRV-NCD of 250 mg/day for EPA+DHA for inclusion in the *Guidelines on Nutrition Labelling* (CAC/GL2-1985).

Despite GOED's conclusion about the totality of available scientific evidence supporting an NRV-NCD for EPA+DHA, like many other Codex Member Countries (CMC) and non-governmental organizations (NGO), GOED has a number of concerns about the NUGAG reports and recognizes the comment period following the distribution of NUGAG's lengthy and in-depth reports was short. Therefore, GOED supports Recommendations 1-3 of the eWG Report to continue the work over the next year in order to seek additional advice on a number of issues and to evaluate further evidence upon receipt from NUGAG. In addition, a continuation would allow for the reporting of results from relevant, large clinical studies that are scheduled to finish up at the end of this year. While GOED is

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concerned about the potential for some of the studies to report neutral findings due to their design, the additional results will add to the power of a meta-analysis and the totality of available scientific evidence.

Should the Committee determine a continuation is the best course of action, consideration should be given to involving JEMNU (Joint FAO/WHO Expert Group on Nutrition), the officially recognized scientific body advising CCNFSDU.

SPECIFIC COMMENTS

For ease of reading, GOED's comments are broken into different sections:

- Scientific Evidence Supporting Adoption of an NRV-NCD for EPA+DHA
- NRV-NCDs: EPA+DHA Versus Sodium, Potassium and Saturated Fatty Acids
- CHD Death Definition
- Studies that Should Not Have Been Included in the NUGAG Review
- Basis for NRV-NCD EPA+DHA: Observational Studies Versus RCTs
- Recognized Authoritative Scientific Bodies

Scientific Evidence Supporting Adoption of an NRV-NCD for EPA+DHA

As summarized in Table 1, NUGAG's evidence clearly demonstrates an association between EPA+DHA intake and reduced risk of CHD mortality/fatal CHD events from observational trials and confirms that the effect can be observed in RCTs for pre-planned subgroup analyses, e.g. coronary death.

Table 1. NUGAG RCT vs Cohort Results

RCTs	**#Studies**	**N**	**RR**	**95% CI**
Meta-analysis of the effect of EPA+DHA on CHD deaths	21	73,491	0.93	0.79-1.09
Sensitivity analysis of the effect of EPA+DHA on CHD deaths, omitting studies only reporting cardiac death	21	65,325	0.83	0.74-0.94
Prospective Cohort studies	**#Studies**	**N**	**RR**	**95% CI**
Fatal Coronary Heart Disease	9	5,904	0.81	0.68 to 0.97

In addition, two recent publications, reporting on the results of two different meta-analyses[1,2], commissioned by GOED, in anticipation of the Codex work to establish an NRV-NCD for EPA+DHA, corroborate NUGAG's findings. The relevant outcomes of those publications are summarized in Tables 2 & 3.

Table 2. Alexander et al. 2017

Outcome	# Studies	RR	95% CI
RCTs			
Coronary Death – all RCTs	5	0.81	0.65-1.00
Coronary Death – 2° prevention	4	0.80	0.64-0.99
Prospective Cohort Studies			
Fatal Events	14	0.77	0.66-0.90
Coronary Death	9	0.82	0.69-0.98

Table 3. Maki et al. 2017

Studies	#RCTs	N	RR	95% CI
1° Analysis	14	71,899	0.920	0.863-0.981
1° Analysis Subsets				
>1 g/d EPA+DHA	7	20,418	0.709	0.508-0.990
TG ≥ 150 mg/dL	8	44,008	0.826	0.723-0.944
LDL-C ≥ 130 mg/dL	8	44,188	0.828	0.725-0.946
2° Prevention	10	27,111	0.870	0.801-0.945
Statin use < 40%	9	20,192	0.871	0.801-0.948

Further corroboration is provided by over a dozen meta-analyses over the last 12 years of RCTs of EPA/DHA and CHD mortality risk. All have found statistically significant reductions in risk. See Table 4.

Table 4. Results of Relevant Meta-Analyses Published over the last 12 years (references at end of letter)

Meta-Analysis	Studies	Coronary Death Risk Reduction
Wen et al, 2014	14	12% (p=0.003)
Casula et al, 2013	11	32% (p<0.05)
Trikalinos et al, 2012	14	11% (p<0.05)
Kotwal et al, 2012	20	14% (p=0.03)

[1] Alexander DD, Miller PE, Van Elswyk ME, Kuratko CN, Bylsma LC. A Meta-Analysis of Randomized Controlled Trials and Prospective Cohort Studies of Eicosapentaenoic and Docosahexaenoic Long-Chain Omega-3 Fatty Acids and Coronary Heart Disease Risk. Mayo Clin Proc. 2017 Jan;92(1):15-29. http://www.mayoclinicproceedings.org/article/S0025-6196(16)30681-4/fulltext

[2] Maki KC, Palacios OM, Bell M, Toth PP. Use of supplemental long-chain omega-3 fatty acids and risk for cardiac death: An updated meta-analysis and review of research gaps. J Clin Lipidol. Epub ahead of print 2017 Aug 2. http://www.lipidjournal.com/article/S1933-2874(17)30395-1/pdf

Rizos et al, 2012	20	9% (p=0.01)
Kwak et al, 2012	14	9% (p<0.05)
Delgado-Lista et al, 2012	21	9% (p=0.03)
Chen et al, 2011	10	19% (p<0.05)
Marik et al, 2009	11	13% (p=0.002)
Zhao et al, 2009	8	29% (p=0.05)
Leon et al, 2008	11	20% (p=0.002)
Wang et al, 2006	4	35% (p<0.05)
Studer et al, 2005	12	32% (p<0.001)

NRV-NCDs: EPA+DHA Versus Sodium, Potassium and Saturated Fatty Acids

Summary

Based on a detailed comparison of NUGAG's reports on sodium, potassium, saturated fatty acids and Omega-3 polyunsaturated fatty acids (hereafter 'EPA+DHA'), GOED believes the evidence in support of establishing an NRV-NCD for EPA+DHA is stronger than the evidence that was used to establish the NRV-NCDs for sodium, potassium and saturated fatty acids. This is based on the following observations:

- The WHO systematic reviews of RCTs on disease outcomes for sodium and potassium failed to find any protective effect on disease outcomes and no disease outcomes were considered for the saturated fatty acids review. In contrast, EPA+DHA was found to be protective for CHD mortality, at least under certain conditions, and CHD incidence. Additionally, the risk of bias was considered low in all assessments, but is objectively lower for EPA+DHA than in the sodium and potassium reviews.
- The reviews of prospective cohort trials only found a protective effect against stroke for potassium (GRADE: Low). No protective effect was observed for sodium and no disease outcomes were considered in the saturated fatty acids review. EPA+DHA was found to be protective against CHD mortality, the main outcome for the NRV-NCD discussion (GRADE: Moderate).
- The NRV-NCDs for sodium, potassium and saturated fatty acids are based on the effect of these nutrients on surrogate markers - blood pressure for sodium and potassium and LDL cholesterol for saturated fatty acids.
- The NUGAG report did not adequately address the effect of EPA+DHA on blood pressure, but multiple published systematic reviews have concluded that EPA+DHA reduce blood pressure moderately.

Among sodium, potassium and EPA+DHA, EPA+DHA were the only nutrients to show a protective effect in meta-analyses of RCTs of disease outcomes and a protective effect in prospective cohorts with a quality of evidence at least as strong as increasing potassium intake for stroke prevention, the only other significant effect observed among these nutrients.

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The comparison in detail

The approach taken by NUGAG in analyzing the evidence supporting an NRV-NCD for EPA+DHA does not appear to be consistent with the approach taken for sodium, potassium, and saturated fatty acids. Based on this approach, the evidence in favor of an NRV-NCD for EPA+DHA is in fact stronger than the evidence used in favor of sodium, potassium, and saturated fatty acids.

NRV-NCDs for sodium, potassium and saturated fatty acids are based solely on RCT evidence on surrogate biomarkers. The process used by NUGAG to establish sodium and potassium guidelines was to:

- First conduct a meta-analysis of RCTs on disease outcomes.
- If no effect was found, conduct a meta-analysis of prospective cohorts on disease outcomes.
- If no effect was found, conduct a meta-analysis of RCTs on surrogate biomarkers.

While it is preferable to have solid data based on well-designed interventional trials, in practice, the extreme variability of behavior in people participating in nutritional research often makes these studies underpowered, and recommendations typically consider other forms of evidence.

Because of the strength of the approach used by NUGAG to establish sodium, potassium and saturated fatty acids NRV-NCDs, and for consistency, the same method should be applied to the development of an EPA+DHA guideline and subsequent NRV-NCDs. It is therefore useful to compare the type, quality and strength of the evidence underlying the sodium, potassium and saturated fatty acids NRV-NCDs with the evidence presented by NUGAG for EPA+DHA.

Evidence from RCTs on disease outcomes

Comparing the RCT evidence on hard disease outcomes from the sodium, potassium and saturated fatty acids reviews is important because some of the comments submitted to the eWG noted that EPA+DHA RCT analyses have not established causality. However, in the cases of the sodium, potassium and saturated fatty acids reviews, no sets of assumptions led to statistically significant reductions in relative risk for the disease endpoints of interest (CVD, CHD, etc.), but, with EPA+DHA, statistically significant reductions in the relative risk of CHD mortality were observed under certain scenarios, specifically when trials not reporting full CHD mortality statistics were excluded. In addition, NUGAG missed relevant CHD Death events due to their search strategy and inclusion of those events would also find a statistically significant effect for the overall CHD mortality analysis. See section entitled “CHD Death Definition” for an expanded analysis on this topic.

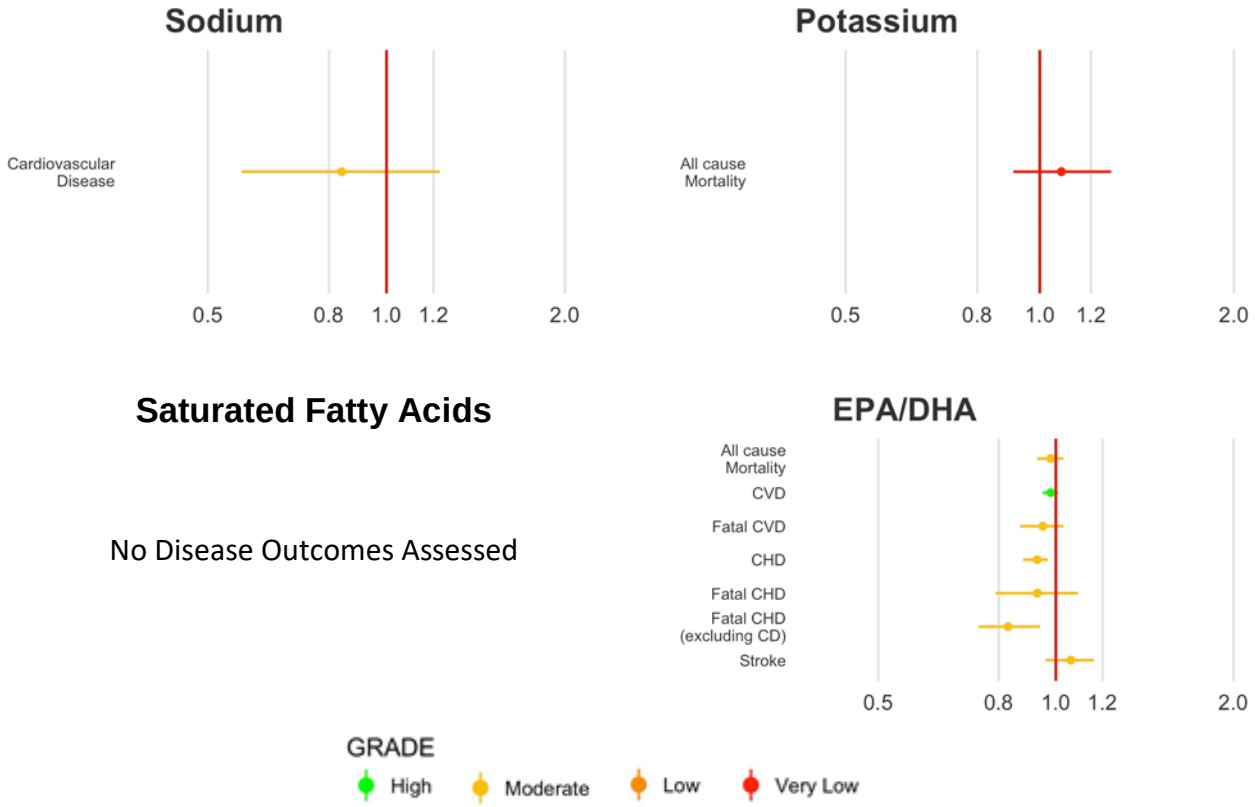
For sodium reduction, NUGAG conducted a meta-analysis whose endpoint was Cardiovascular Disease incidence, failing to find a statistically significant protective effect (RR: 0.84; 0.57 – 1.23). Other disease endpoints were considered, but could not be evaluated, either due to a lack of available RCTs or an insufficient number of events.

The situation is similar for potassium, for which it was only possible to estimate the effect of increased intake on the risk of all-cause mortality. The analysis did not find a statistically significant protective effect (RR: 1.08; 0.91 – 1.29).

No disease outcomes were evaluated for saturated fatty acids.

For EPA+DHA, meta-analysis of RCTs on disease outcomes revealed a protective effect for CHD (RR: 0.93; 0.88 – 0.97) and CHD mortality under certain assumptions, including omitting trials only reporting cardiac death (RR: 0.83; 0.74 – 0.94).

The following figure displays the relative risk and 95% confidence interval for all primary cardiovascular disease outcomes considered in the sodium or potassium guidelines, or the systematic reviews conducted by NUGAG on EPA+DHA and saturated fatty acids. The results are color-coded according to NUGAG's assessment of the GRADE Quality of Evidence score.

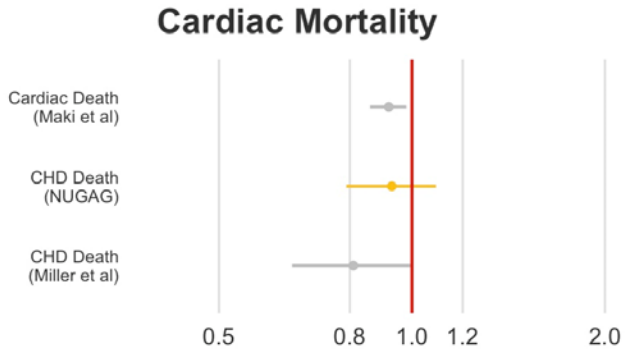


In all cases, the summary meta-analyses were underpowered, but only in the cases of sodium, potassium and saturated fatty acids was there any explicit discussion of power.

NUGAG's CHD mortality analysis of EPA+DHA RCTs is underpowered. Statistical power can be defined as the probability that a study will reach a statistically significant positive conclusion, if there is indeed a protective effect. Most readers of this report will assume that if there is a true effect, then this study would have a good chance of detecting it. In fact, that is not the case – a real effect of this size would be unlikely to be detected given the number of participants. Between the two groups, there

were 73,041 subjects. The risk in the omega-3 group is 2.09% ((773 events/36836 subjects) *100), the risk in the control is 2.24% ((823 events/36655 subjects) *100), RR = 0.93. Detecting an effect at the same risk ratio, with a p-value significance cutoff of 0.05, with 80% power would require ~155,000 subjects per group.

The exclusion of relevant outcomes, due to the unusual CHD definition in NUGAG's EPA+DHA analysis, affected the power of this study, which can be observed in the scenarios where statistically significant associations were found when the event rates were higher. The authors of the report correctly observe that the results of a meta-analysis will depend on the assumptions made. Few assumptions are more consequential than choices concerning the definition of outcomes. Other recently published meta-analyses on cardiac death (using different outcome definitions) have found different estimates of risk. The studies by Maki *et al.*[3] and by Alexander *et al.*[4] did not report a GRADE score, but according to GOED's analysis, such an analysis would likely result in a *Moderate* rating for both studies.



Regardless, there are a couple of large-scale RCTs due to be completed in the next year in both primary and secondary prevention that will report on CHD mortality and will nearly double the number of subjects that can be analyzed, significantly increasing the power of any analysis.

Study	Est. Completion	Subject Enrolment
ASCEND	September 2017	15,480
REDUCE-IT	December 2017	8,000
VITAL	June 2018	25,871
STRENGTH	October 2019	13,086

Source: Clinicaltrials.gov

[3] Maki KC, Palacios OM, Bell M, Toth PP. Use of supplemental long-chain omega-3 fatty acids and risk for cardiac death: An updated meta-analysis and review of research gaps. J Clin Lipidol. Epub ahead of print 2017 Aug 2. http://www.lipidjournal.com/article/S1933-2874(17)30395-1/pdf

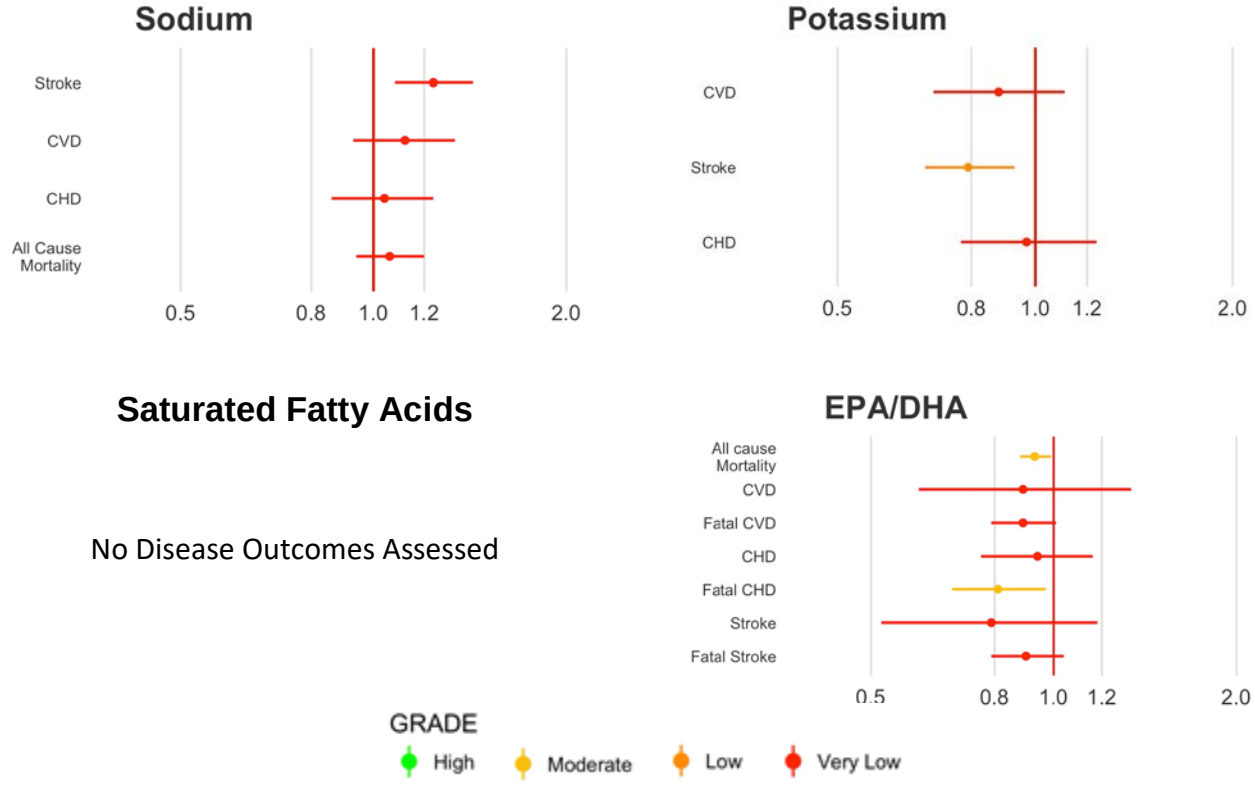
[4] Alexander DD, Miller PE, Van Elswyk ME, Kuratko CN, Bylsma LC. A Meta-Analysis of Randomized Controlled Trials and Prospective Cohort Studies of Eicosapentaenoic and Docosahexaenoic Long-Chain Omega-3 Fatty Acids and Coronary Heart Disease Risk. Mayo Clin Proc. 2017 Jan;92(1):15-29. http://www.mayoclinicproceedings.org/article/S0025-6196(16)30681-4/fulltext

The NUGAG reports on sodium and potassium recognize that their analyses of RCT evidence is underpowered, and therefore it is necessary to consider other sources of information (including prospective cohort studies and validated biomarker data) to develop NRV-NCDs. It seems reasonable to do the same for EPA+DHA, particularly keeping in mind that the RCT evidence for EPA+DHA is stronger than the evidence for sodium, potassium, or saturated fatty acids.

Evidence from Cohort Studies on disease outcomes

Nearly all prospective cohort analyses for sodium and potassium failed to demonstrate a statistically significant reduction in the relative risk for the disease outcomes of interest, but did find significant effects for EPA+DHA on CHD mortality. There was a single outcome for potassium that demonstrated a protective effect on stroke, albeit with a low quality (GRADE) base of evidence. EPA+DHA demonstrated a significant protective effect based on a moderate GRADE of evidence. When evaluating the quality of evidence, NUGAG uses a subset of the criteria proposed by the GRADE Working Group, and as a result, no systematic review of cohort trials can reach a higher score. *None* of the analyses for the sodium or potassium reviews reached this quality level (and the review for saturated fatty acids did not address disease outcomes, only biomarkers).

The following figure displays the relative risk and 95% confidence interval for all primary cardiovascular disease outcomes considered in the sodium or potassium guidelines, or the systematic reviews conducted by NUGAG on saturated fatty acids and EPA+DHA. The plots contain every disease outcome considered in the sodium and potassium guidelines and the systematic reviews conducted by NUGAG on saturated fatty acid and EPA+DHA.



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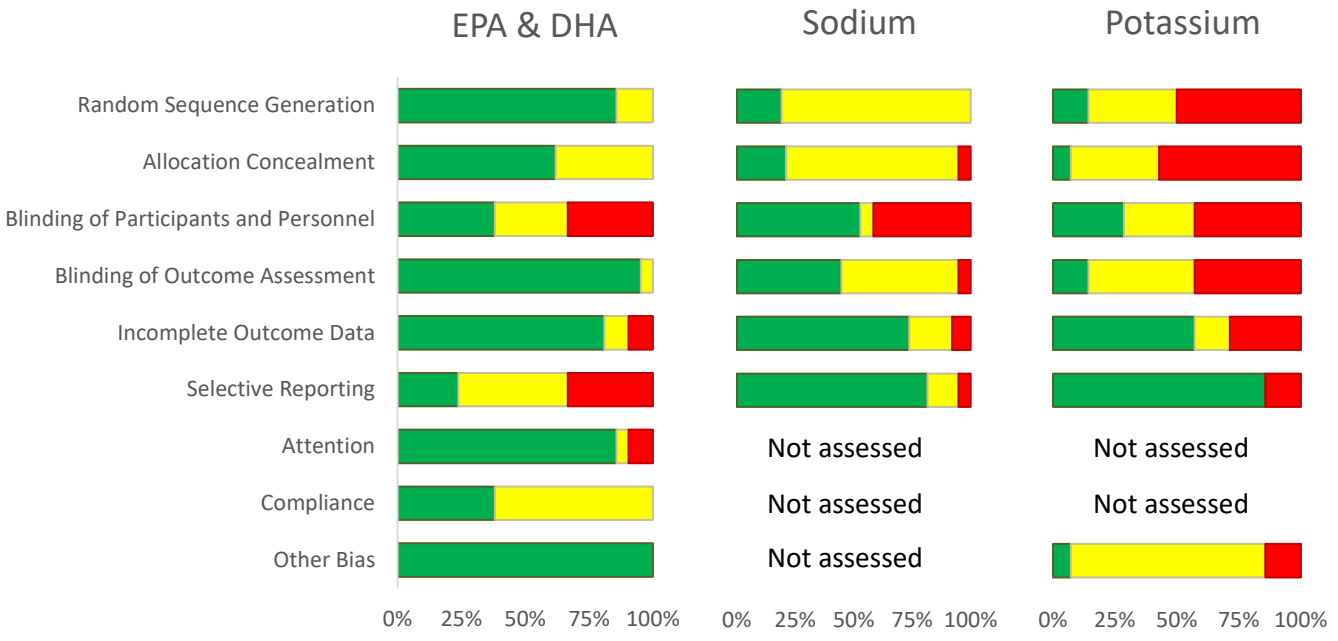
Evidence from RCTs on Surrogate Biomarkers

NRV-NCDs for sodium, potassium and saturated fatty acids appear to be established solely on the basis of surrogate biomarker RCT evidence and the effects were only observed for sodium and potassium on blood pressure and for saturated fatty acids on LDL cholesterol. No effect was observed for EPA+DHA on surrogate markers, but was observed for triglycerides. In all cases, rather than conduct a systematic literature search for studies, NUGAG used only studies that also reported CVD or CHD disease outcomes, giving an incomplete view of the totality of the scientific evidence for these markers. For EPA+DHA, multiple published systematic reviews have included systematic literature searches beyond the outcomes included in the NRV report and have concluded that EPA+DHA reduce blood pressure moderately.[5,6,7]

Risk of Bias

The summary risk of bias assessments from NUGAG are similar for EPA+DHA, sodium and potassium RCTs. In all three reviews, NUGAG concluded there was an overall low risk of bias in the base of evidence. By comparing the summary risk of bias graphs side-by-side, one might argue the risk of bias is lower in the EPA+DHA review than in the sodium or potassium analyses (see below); however, in the EPA+DHA review, NUGAG decided, despite an overall low risk of bias, that only the individual studies with a low risk of bias should be relied upon in its analysis of CHD mortality, while the studies of moderate to high risk of bias should be ignored.

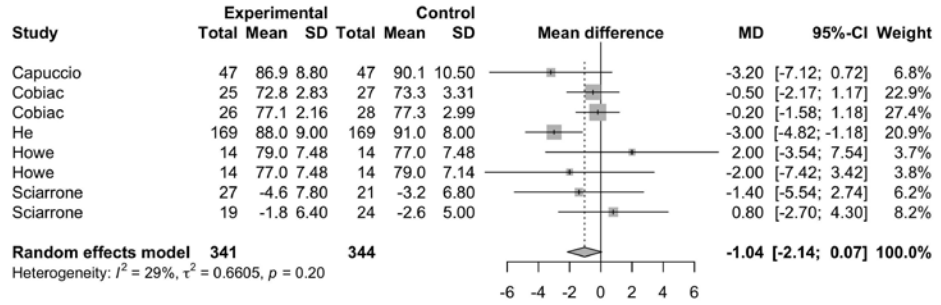


[5] Campbell F, Dickinson HO, Critchley JA, Ford GA, Bradburn M. A systematic review of fish-oil supplements for the prevention and treatment of hypertension. Eur J Prev Cardiol 2013; 20:107–120.
[6] Hartweg J, Farmer AJ, Holman RR, Neil HAW. Meta-analysis of the effects of n-3 polyunsaturated fatty acids on haematological and thrombogenic factors in type 2 diabetes. Diabetologia 2007; 50:250–258.
[7] Miller PE, Van Elswyk M, Alexander DD. Long-chain omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and blood pressure: a meta-analysis of randomized controlled trials. Am J Hypertens 2014; 27:885-96.

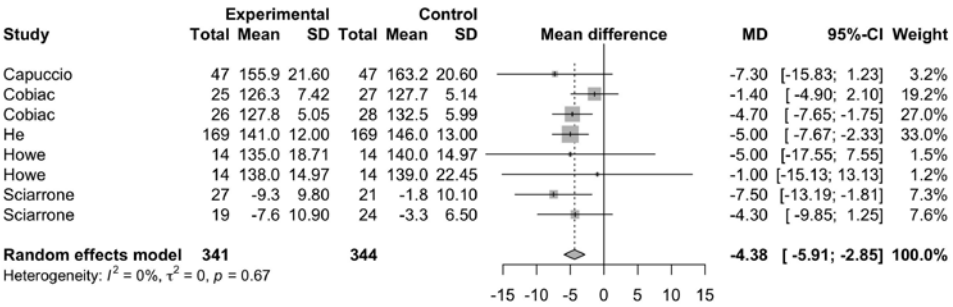
This approach has three primary issues. **First**, the authors determined the overall risk of bias of individual studies primarily by their random sequence generation, blinding, and allocation concealment domains, rather than considering other domains of bias that could have a greater impact on the outcome, as noted in the European Union's comments to the eWG.

Second, this type of analysis is inconsistent with both the sodium and potassium reviews. NUGAG did not conduct this kind of sensitivity analysis in the sodium, potassium and saturated fatty acids reviews. Had they relied upon only studies with low risk of bias based on those three domains, they would have likely concluded that the results for sodium in diastolic blood pressure reduction were driven by moderate and high risk of bias studies, and potassium and saturated fatty acids were not assessable because NO studies were considered at low risk of bias individually. The effect of sodium reduction on systolic blood pressure is the only outcome where studies at low risk of bias have showed a significant effect in any of these reviews. The forest plots below show the effects of sodium on systolic and diastolic blood pressure for studies at low risk of bias in the sequence generation, blinding and allocation concealment domains.

Effects of sodium reduction on diastolic blood pressure



Effects of sodium reduction on systolic blood pressure



Third, in the report of RCTs on the health effects of omega-3 PUFAs, specifically for EPA+DHA, NUGAG visually compared the low risk of bias studies to those of moderate to high risk of bias and concluded that the results differed. This approach conflicts with the well-established practice of conducting a meta-regression using risk of bias as a predictor, as recommended by the Cochrane Collaboration. GOED conducted this analysis, and found no statistically significant difference in any of the bias domains considered. See Table 5.

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Table 5. Meta-regression of Risk of Bias based on Individual Bias Domain

Bias Domain	Meta-regression p-value
Randomization	0.832
Concealment	0.841
Blinding of Participants and Personnel	0.655
Blinding of Assessors	0.322
Attrition	0.886
Reporting	0.760
Attention	0.552
Compliance	0.469
Other	n/a*

* All studies at low risk of "Other" bias

Summary Comparison Sodium, Potassium, Saturated Fatty Acids and EPA/DHA Reviews
The below table shows how the evidence in support of establishing an NRV-NCD for EPA+DHA is stronger than the evidence that was used to establish the NRV-NCDs for sodium, potassium and saturated fatty acids.

		Did the reviews of…			
		EPA+DHA	**Sodium**	**Potassium**	**Saturated Fatty Acids**
…demonstrate significant effects in…	**RCTs of Disease Endpoints**	**Yes** *CHD and Some CHD Mortality Analyses*	**No**	**No**	**N/A**
	Prospective Cohorts	**Yes** *CHD Mortality*	**No**	**Yes** *Stroke*	N/A
	RCTs of Markers	**Yes** *Triglycerides*	**Yes** *Blood Pressure*	**Yes** *Blood Pressure*	**Yes** *LDL Cholesterol*

The text color indicates the GRADE score: Green = High, Yellow = Moderate, and Red = Very Low

CHD Death Definition

As mentioned previously, relevant Fatal CHD events were missed in the NUGAG review due to its definition of this outcome. The NUGAG RCT and Maki et al. reviews included data from 21 and 20 studies, respectively, with 16 studies common between the two. Although pre-defined for both reviews, the events considered of relevance were not always the same between the reports of Maki et al. and NUGAG. Maki et al. included myocardial infarction (MI) (fatal), sudden cardiac death, sudden cardiac mortality, coronary mortality, cardiac mortality, or ischemic heart disease (IHD) mortality. NUGAG included data reported as coronary deaths, or where these were not reported, IHD death, fatal MI or cardiac death (using the first of these available in any study). For this reason, the authors in the

respective reviews extracted a different number of mortality events for six of the 16 common studies in their analyses. See Table 6.

Table 6. Events numbers as reported by Maki et al. and NUGAG *for Studies in Common*[1]

Study	O-3 Events Maki et al.	O-3 Events NUGAG	Control Events Maki et al.	Control Events NUGAG
Sacks et al., 1995	0	0	1	1
Gissi-P	228	214 (-14)	292	265 (-27)
Von Schacky et al., 1999	0	0	1	1
Nilsen et al., 2001	8	8	8	8
JELIS	29	29	31	31
GISSI-HF	613	20 (-593)	661	25 (-636)
Rauch et al., 2010	28	67 (+39)	29	51 (+22)
Einvik et al, 2010	3	0 (-3)	7	2 (-5)
Roncaglioni et al., 2013	101	82 (-19)	95	76 (-19)
Bonds et al., 2014	12	3 (-9)	9	0 (-9)
Total	**1022**	**423**	**1134**	**460**

[1]Note: Maki et al. also included ORIGIN (Bosch et al., 2012) contributing 574 and 581 events, respectively, not included by NUGAG. All others studies included by Maki et al., but not by NUGAG, are likely inconsequential due to small event numbers.

GOED believes the definitions used by NUGAG are incorrect, and that their use artificially and dramatically reduces the number of events included in the analysis. As the NUGAG report states, “any effect of LCn3 on CHD deaths appears to depend on assumptions made in analyses”. The choices made by NUGAG on the outcome definitions and the list of relevant trials take an underpowered meta-analysis, and erodes the power even further.

The treatment of GISSI-HF[8] may provide the best example of how NUGAG's definition of CHD death erodes statistical power. NUGAG's definition of CHD death prioritized coronary death, but if this outcome was not directly reported for a particular trial, they used in order of preference – IHD death, fatal MI or cardiac death in a mutually exclusive manner. The authors of the primary GISSI-HF publication, Tavazzi et al. reported 307 and 325 sudden cardiac deaths for n-3 fatty acids and control, respectively. The authors also report 20 and 25 deaths due to acute MI for n-3 fatty acids and control, respectively. Because NUGAG selected only one of three substitutes for coronary death (rather than summing all related) and prioritized fatal MI over cardiac death (assuming sudden cardiac death was part of their definition of cardiac death), they used the 20 and 25 events in their analysis rather than

[8] Tavazzi L, et al. (2008) Effect of n-3 polyunsaturated fatty acids in patients with chronic heart failure (the GISSI-HF trial): a randomised, double-blind, placebo-controlled trial. Lancet 372, 1223–1230. http://www.thelancet.com/pdfs/journals/lancet/PIIS0140-6736(08)61239-8.pdf

the 307 and 325 events. NUGAG's mutually exclusive interpretation of the term "or" means they left out relevant CHD mortality events from their analysis.

Another example is the ORIGIN[9] study, which NUGAG included in meta-analyses on every outcome except CHD mortality. This appears to be due to NUGAG's unique outcome definitions - "included data reported as coronary deaths, or where these were not reported, IHD death, fatal MI or cardiac death (using the first of these available in any study)". As a result, 288 and 259 sudden cardiac deaths for n-3 fatty acids and control, respectively were not included. Notably, inclusion of this study would reduce the benefit of n-3 fatty acids relative to placebo, but would also reduce the confidence intervals and improve the power of the study.

As mentioned in the section entitled "NRV-NCDs: EPA+DHA Versus Sodium, Potassium and Saturated Fatty Acids", a real effect of the size observed in the primary analysis was unlikely to be detected given the number of participants – 73,041 between the two groups. Detecting an effect at the same risk ratio, with a p-value significance cutoff of 0.05, with 80% power, would require ~155,000 subjects per group. Note that NUGAG's meta-analysis of the effect of EPA+DHA on CHD deaths, omitting studies only reporting cardiac death, was statistically significant despite including fewer subjects and events, because the relative risk was lower, which increased power. There is no discussion about the statistical power of the CHD mortality analysis in the NUGAG report, nor any of the subgroup analyses.

Because NUGAG's primary RCT meta-analysis on CHD mortality is underpowered, it is impossible to determine whether the fact that the protective effect of EPA and DHA failed to reach statistical significance was due to a real lack of a protective effect, or just to the fact that the combined number of participants and/or CHD mortality events was too low. Given the evidence for a protective effect shown by observational trials and RCTs, the latter seems more likely. The conclusion reached by NUGAG researchers that EPA and DHA do not protect against CHD mortality is thus unsupported.

While it is uncertain if the decision to limit the number of events reported for an outcome is solely responsible for NUGAG's observation of diminished strength of the relationship between EPA+DHA intake and reduction of fatal CHD events, the Maki et al. meta-analysis, as well as a number of other meta-analyses (see Table 4), published over the last 12 years, suggest this may be the case.

Studies that Should Not Have Been Included in the NUGAG Review

- NUGAG included the Alpha Omega Trial[10], which compares an intervention of EPA+DHA to a composite group that included the placebo and alpha linolenic acid (ALA) interventions. Since the ALA intervention had a protective effect in this study, this increased the effect of the control comparison and makes it impossible to extract the true effect of EPA+DHA versus placebo.

[9] ORIGIN Trial Investigators, Bosch J, Gerstein HC, Dagenais GR, et al. n-3 fatty acids and cardiovascular outcomes in patients with dysglycemia. N Engl J Med. 2012;367(4):309-318. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1203859

[10] Kromhout D, Giltay EJ, Geleijnse JM; Alpha Omega Trial Group. n-3 fatty acids and cardiovascular events after myocardial infarction. N Engl J Med 2010; 363:2015-26.

- The NUGAG analysis included RCTs where the intervention was dietary advice, rather than an EPA+DHA product. At the very least, a sensitivity analysis excluding these trials (DART1[11] and DART2[12]) should be conducted to determine if it affects the conclusion. GOED has done this analysis and excluding these studies strengthens the effect and tightens the confidence intervals (see below). In addition, DART1 and DART2 account for most of the heterogeneity in NUGAG's analysis, yet there is no discussion by NUGAG of how including trials on dietary advice impact the quality of the results for EPA+DHA interventions.
    - NUGAG analysis with DART1 and DART2: RR = 0.93 (0.79-1.09), I^2 = 35%
    - NUGAG analysis without DART1 and DART2: RR = 0.91 (0.81-1.02), I^2 = 0%

Basis for NRV-NCD EPA+DHA: Observational Studies Versus RCTs

GOED believes data generated from RCTs should not be solely relied upon as the primary means to quantitatively establish NRVs. Every study design has strengths and weaknesses, and we think it is desirable to take advantage of the totality of evidence when developing guidelines.

The main benefit of an RCT is that it allows the establishment of a direct cause and effect relationship between a nutrient and a health effect. No other study design can accomplish this, but this advantage comes at a cost. Because conducting an interventional study is expensive, RCTs tend to have a comparatively small number of subjects (often at a high risk), and be relatively short. As a result, RCTs (and meta-analyses of RCTs) often fail to find a significant effect. Perhaps more importantly, RCTs are often conducted on high-risk populations, using relatively high doses and often tracking compliance. These strategies are used to increase the power of the study by increasing the magnitude of the effect, but they make it difficult to extrapolate the results to the general population. It bears mentioning that these choices are made often because the researchers want to prove a cause-effect relationship, rather than to establish quantitative intake targets or determine the effect of increased intake in a general population.

Prospective cohort trials, on the other hand, have the benefit of including more participants, and following them for a longer period, and of being conducted in a more representative sample of the general population and under more normal conditions. Because of that, they are more useful at establishing the expected public health effect of a proposed intervention, and at determining the optimal intake level of a nutrient.

We believe that it makes sense to use the strengths of both study types. If prospective cohorts can identify an association and causality can be confirmed via RCTs, then prospective cohort data can be used to establish quantitative intake targets even if the study design of RCTs does not reflect the intended use of the quantitative intake target. If, additionally, RCTs show that the nutrient under

[11] Burr ML, Fehily AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC, Deadman NM. Effects of changes in fat, fish, and fibre intakes on death and myocardial reinfarction: diet and reinfarction trial (DART). Lancet 1989; 2:757-61.

[12] Burr ML, Ashfield-Watt PA, Dunstan FD, Fehily AM, Breay P, Ashton T, Zotos PC, Haboubi NA, Elwood PC. Lack of benefit of dietary advice to men with angina: results of a controlled trial. Eur J Clin Nutr; 2003; 57:193-200.

consideration modifies a validated risk biomarker, then this provides additional evidence of a true cause-effect relationship.

With respect to EPA+DHA, prospective cohorts show a clear association between moderate EPA+DHA intake and a reduced risk of CHD death. High dose RCTs can be used to confirm such an effect exists because a higher dose can increase the power by increasing the magnitude of an effect, which makes it possible to determine the existence of an effect using fewer subjects. A complete review of RCTs on the effect of EPA+DHA intake on validated biomarkers, particularly blood pressure, could be invaluable in establishing causality.

As mentioned, the strength of RCTs is in proving causality, in this case establishing that the benefits observed in cohort trials are indeed due to EPA+DHA, instead of to other possible benefits of fish intake. This is an important consideration and another reason that dietary intake studies like DART1 and DART2 should not be included in a meta-analysis of RCTs seeking to establish causality of an intervention. Because the intervention is dietary advice, these studies don't help in addressing whether EPA+DHA are responsible for the observed health effects.

We also believe it is plausible that the mechanisms underlying a primary CHD event are the same as a secondary CHD event, which seems to justify combining the two types in a meta-analysis to establish causality. While this approach increases the event rate and thus the power, medications for secondary prevention may decrease the effect of EPA+DHA and introduce a confounder and thus decrease power. At the end of the day, though, the distinction between primary and secondary prevention is blurry at best and we share some of your concerns.

Recognized Authoritative Scientific Bodies

GOED supports the inclusion of the United States as a Recognized Authoritative Scientific Body (RASB) as mentioned in last year's discussion paper on the Proposed Draft NRV-NCD for EPA and DHA Long Chain Omega-3 Fatty Acids (CX/NFSDU 16/38/8). In the United States, the Dietary Guidelines for Americans is "the cornerstone of Federal nutrition policy and nutrition education activities.[13]" The Dietary Guidelines for Americans 2015-2020[14] include the following statement (see page 23), "For the general population, consumption of about 8 ounces per week of a variety of seafood, which provide an average consumption of 250 mg per day of EPA and DHA, is associated with reduced cardiac deaths among individuals with and without preexisting CVD." The aforementioned statement in the Dietary Guidelines is based on the Nutrition Evidence Library (NEL) review entitled "Specific Fats, Fatty Acids, and Cholesterol-Seafood N-3 Fatty Acids and Risk of Cardiovascular Disease[15] (starts on page 129)."

[13] https://www.cnpp.usda.gov/dietary-guidelines
[14] https://health.gov/dietaryguidelines/2015/resources/2015-2020_Dietary_Guidelines.pdf
[15] https://www.cnpp.usda.gov/sites/default/files/usda_nutrition_evidence_flbrary/2010DGAC-SR-FattyAcidsAndCholesterol.pdf

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