CODEX ALIMENTARIUS COMMISSION

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**Agenda Item 6** **NFSDU/39 CRD/09**

**Original language only**

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

**Thirty-ninth Session**

**Berlin, Germany**
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# REPORT OF ELECTRONIC WORKING GROUP ON ESTABLISHING NRV-NCD FOR EPA AND DHA (DRAFT)

*Comments of the European Union, Thailand, Global Organization for EPA and DHA Omega-3s (GOED)*

## EUROPEAN UNION

***European Union competence***

***European Union vote***

The European Union (EU) would like to thank Chile and the Russian Federation for coordinating the working group in which the EU participated.

The EU has the following preliminary comments on the Draft NRV-NCD for EPA and DHA long chain omega-3 fatty acids, in relation to the Report of the Electronic Working Group on Establishing NRV-NCD for EPA and DHA (Draft).

The EU supports the recommendations 1, 2 and 3. An extended commenting period may provide additional input to the discussion. However, scientific evidence should be discussed and analysed by a risk assessor, a scientific group of experts, as the issues under consideration are highly technical.

## THAILAND

**General comments**

There are NUGAG's comments with some arguments that the evidence was not strong enough to set up NRV-NCD for EPA/DHA.

In the conclusions at the end of this document, there are several recommendations which will require much more time for discussion, we are not so sure that the CCNFSDU will have time for this particularly the source of EPA/DHA whether they come from foods or food supplements. In this regard it is suggested that this matter should be referred to NUGAG or JEMNU to review again of all scientific evidences including the latest recommendations by the RASBs.

## GLOBAL ORGANIZATION FOR EPA AND DHA OMEGA-3S (GOED)

**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 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 |

[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

| | | | |
|---|---|---|---|
| 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) |
| 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.

**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.

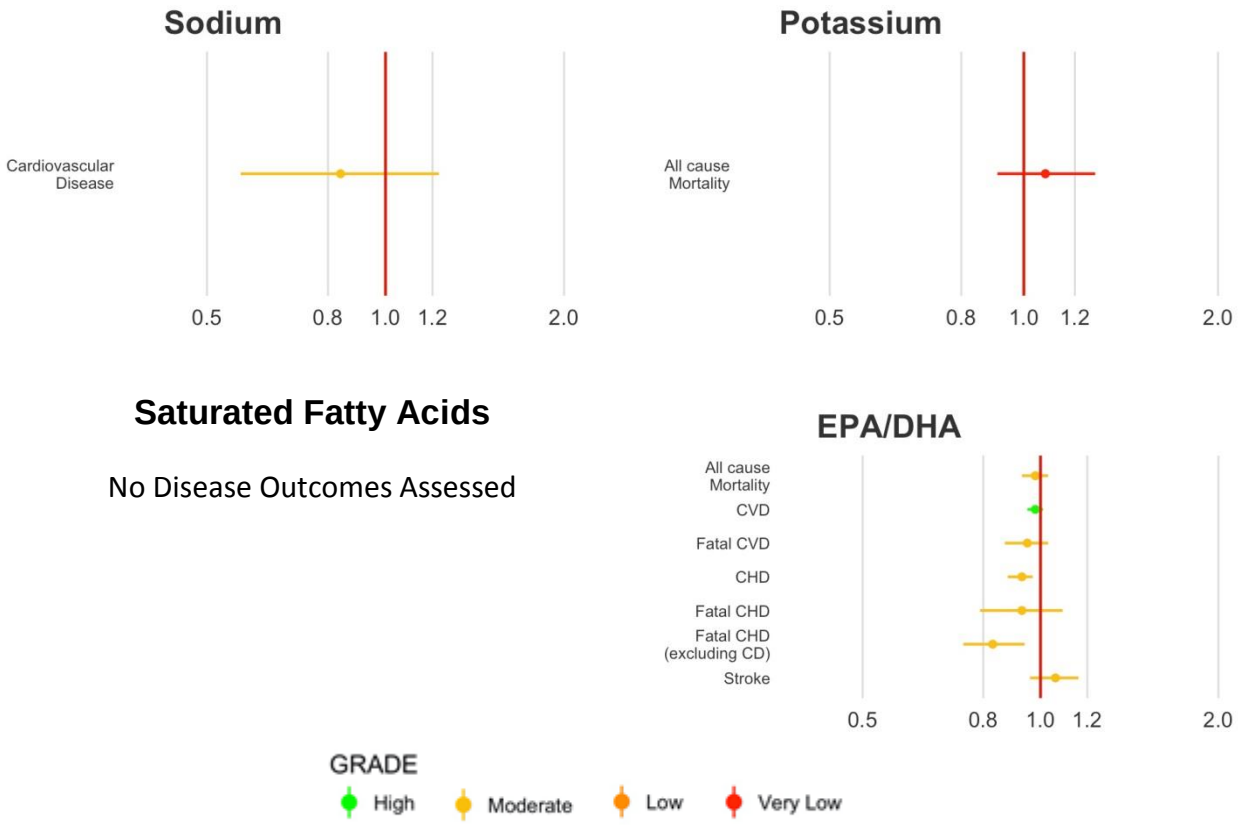
For sodium reduction, NUGAG conducted a meta-analysis whose endpoint was Cardiovascular Disease incidence, failing to find a statistically significant protective effect (RR: 0.84; 0.57 – 1.23). Other disease endpoints were considered, but could not be evaluated, either due to a lack of available RCTs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



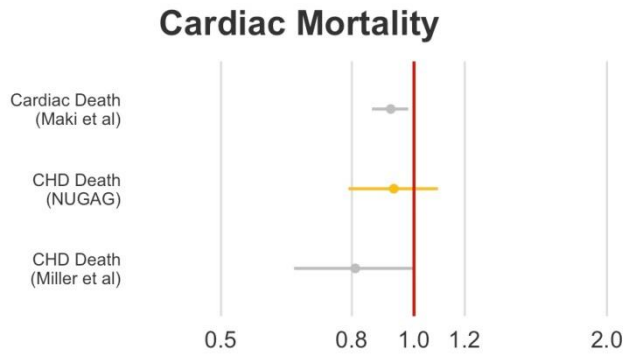

In all cases, the summary meta-analyses were underpowered, but only in the cases of sodium, potassium and saturated fatty acids was there any explicit discussion of power.

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.

[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




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 |

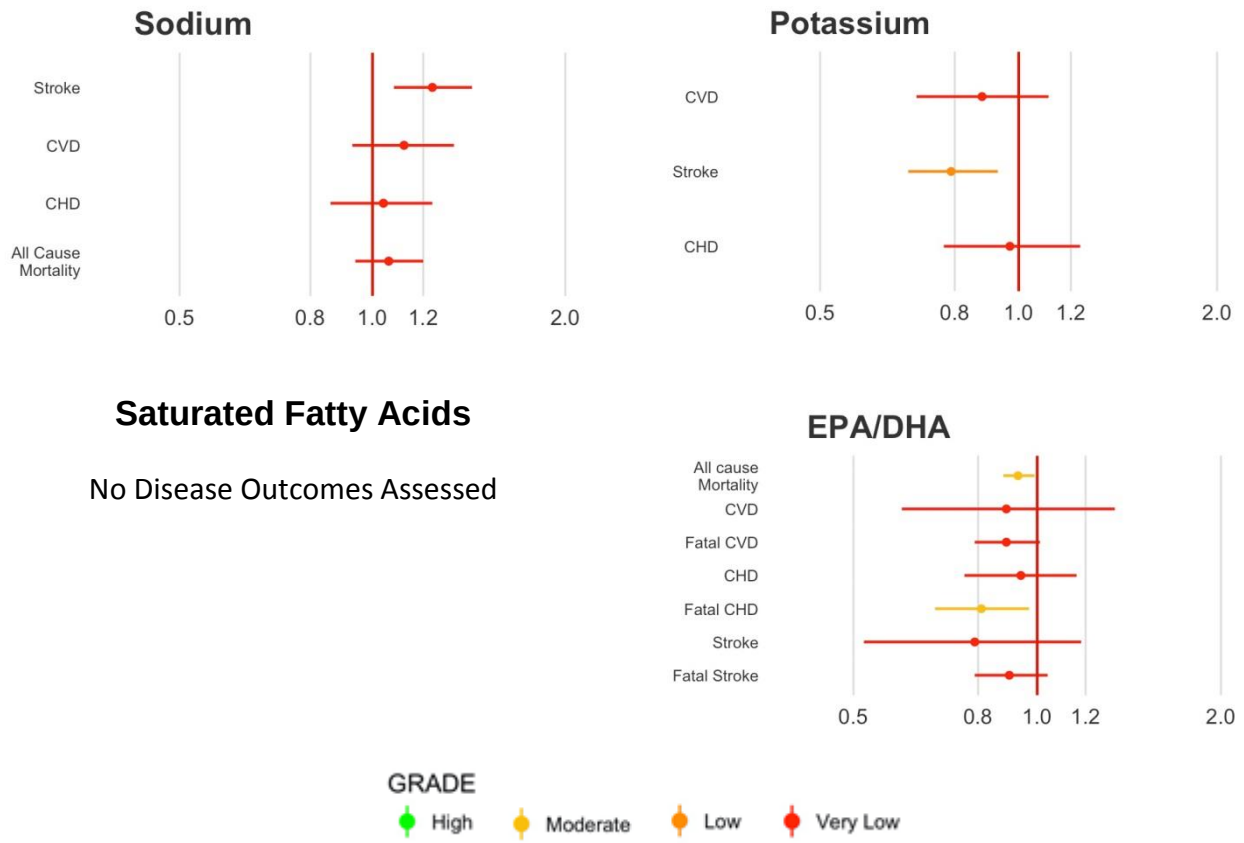
*Source: Clinicaltrials.gov*

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.



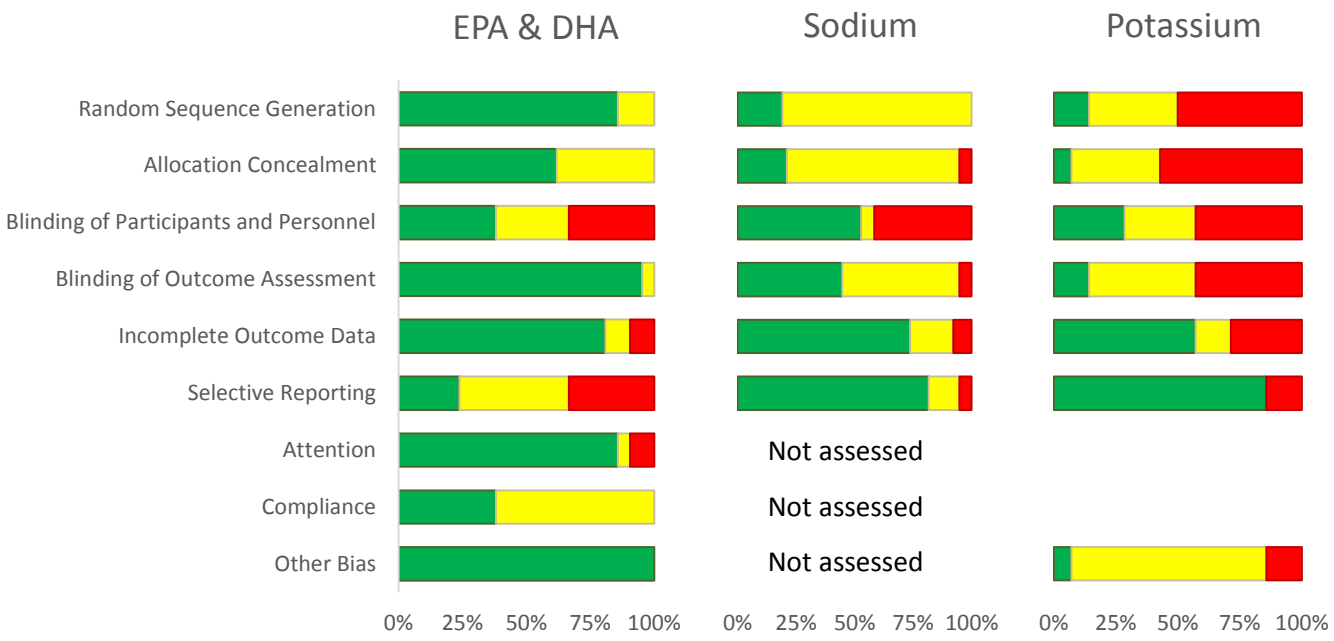

*Evidence from RCTs on Surrogate Biomarkers*

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.

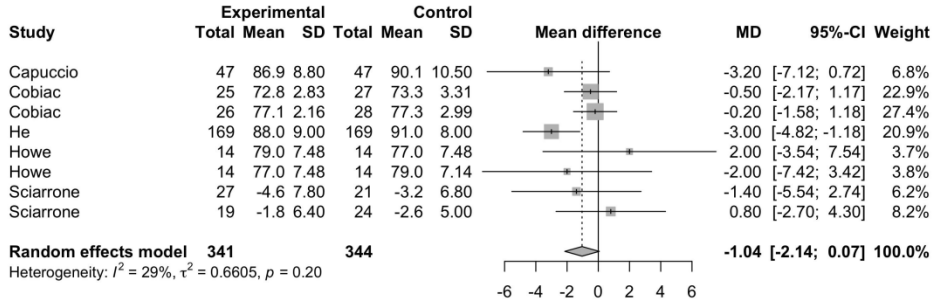
[5] Campbell F, Dickinson HO, Critchley JA, Ford GA, Bradburn M. A systematic review of fish-oil supplements for the prevention and treatment of hypertension. Eur J Prev Cardiol 2013; 20:107–120.
[6] Hartweg J, Farmer AJ, Holman RR, Neil HAW. Meta-analysis of the effects of n-3 polyunsaturated fatty 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.



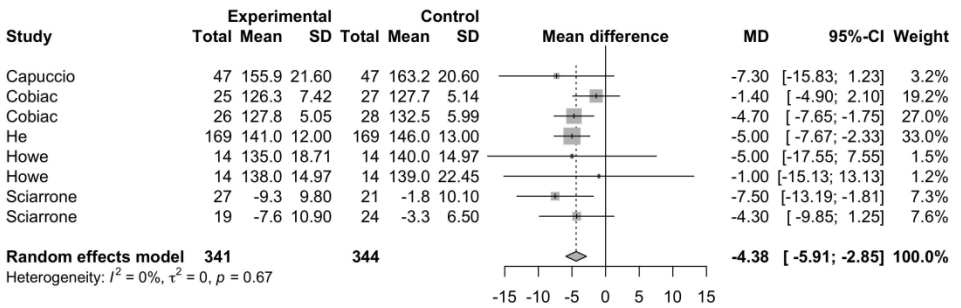

This approach has three primary issues. **First**, the authors determined the overall risk of bias of individual studies primarily by their random sequence generation, blinding, and allocation concealment domains, rather than considering other domains of bias that could have a greater impact on the outcome,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

**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… analyses of…*** | **RCTs of Disease Endpoints** | **Yes**<br>*CHD and Some CHD Mortality Analyses* | **No** | **No** | **N/A** |
| | **Prospective Cohorts** | **Yes**<br>*CHD Mortality* | **No** | **Yes**<br>*Stroke* | N/A |
| | **RCTs of Markers** | **Yes**<br>*Triglycerides* | **Yes**<br>*Blood Pressure* | **Yes**<br>*Blood Pressure* | **Yes**<br>*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 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

[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

[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

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

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[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.

[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.

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)."

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[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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