



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

Fortieth Session

Berlin, Germany

26 – 30 November 2018

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

*Comments of GOED*

#### GOED - Global Organization for EPA and DHA Omega-3s

Since August, results from three large-scale clinical trials assessing EPA and/or DHA supplementation have been reported, including: A Study of Cardiovascular Events in Diabetes (ASCEND), Vitamin D and Omega-3 Trial (VITAL), and Reduction of Cardiovascular Events with EPA – Intervention Trial (REDUCE-IT). All of these have added positively to the body of evidence supporting the benefits of omega-3.

- ASCEND reports an 18% statistically significant reduction in risk of vascular death and a 21% risk reduction for coronary death in response to 840 mg EPA+DHA daily in patients with diabetes who are not known to have arterial disease.
- VITAL reports statistically significant risk reductions in total myocardial infarction (MI) (28%); total coronary heart disease (CHD) (17%); and fatal MI (50%) in response to 840 mg EPA+DHA daily. The greatest reductions were demonstrated in those with low dietary fish intake and in African Americans.
- REDUCE-IT reports statistically significant risk reductions in the primary endpoint of major adverse cardiovascular events (MACE) (25%); cardiovascular death or nonfatal MI (25%); fatal or nonfatal MI (31%); and cardiovascular death (20%) in response to 3,840 mg EPA daily.

Results from these trials are an important contribution to the totality of evidence supporting an NRV-NCD for EPA-DHA, and have yet to be considered collectively with the evidence previously reviewed by NUGAG. The results of these trials are relevant to the establishment of the NRV-NCD for EPA-DHA, and none of the studies' results would suggest at any point or interpretation that there is necessary evidence to support a discontinuation of this work.

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.

At the 40<sup>th</sup> Session of the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) to be held in Berlin, Germany from 26-30 November 2018, the Proposed Draft NRV-NCD for EPA and DHA long chain omega-3 fatty acids will be discussed as Agenda Item #7. Despite GOED's opinion that the totality of the available scientific evidence supports the adoption of an NRV-NCD for EPA+DHA for inclusion in the Guidelines on Nutrition Labelling (CAC/GL2-1985)<sup>1</sup>, due to a lack of consensus, we support recommendation #1 of the electronic working group (eWG) to postpone further discussion on this agenda item until new convincing/generally accepted evidence becomes available.

Since August, results from three large-scale clinical trials have been reported, including: A Study of Cardiovascular Events in Diabetes (ASCEND), Vitamin D and Omega-3 Trial (VITAL), and

<sup>1</sup>[http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252Fstandards%252FCAC%252FBGL%252B2-1985%252FCXG\\_002e.pdf](http://www.fao.org/fao-who-codexalimentarius/sh-proxy/en/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252Fstandards%252FCAC%252FBGL%252B2-1985%252FCXG_002e.pdf)

Reduction of Cardiovascular Events with EPA – Intervention Trial (REDUCE-IT). All three studies have added positively to the body of evidence supporting the benefits of omega-3s. Below, GOED provides a summary of the three studies, not to change Delegations' minds about postponing further discussion, but to ensure that none of the studies are misinterpreted to support a discontinuation of work on the NRV-NCD for EPA+DHA. It's important to look at these three trials based on the results that are relevant to the Codex NRV discussion and not rely solely on the media who typically report on primary outcomes only.

### **A Study of Cardiovascular Events in Diabetes (ASCEND)<sup>2</sup>**

ASCEND evaluated, among other things, if supplementation with 840 mg daily of EPA+DHA (omega-3-acid ethyl esters) versus placebo prevents "serious vascular events" (i.e. non-fatal heart attack, non-fatal stroke or transient ischaemic attack, or death from vascular causes) in patients with diabetes who are not known to have arterial disease. Subjects included over 15,000 men and women.

While the authors concluded, "there was no significant difference in the risk of serious vascular events between those who were assigned to receive n-3 fatty acid supplementation and those who were assigned to receive placebo," there's more to the story. The authors also reported an 18% statistically significant reduction in risk of vascular death, which is a relevant finding given that vascular death is one of the components of the primary outcome. Unfortunately, the authors' incomplete conclusion perpetuates the mistaken notion that EPA and DHA provide no benefit.

To date, the most consistently demonstrated and reported benefit associated with omega-3s is the reduction in risk of cardiac death, which includes death from coronary heart disease (CHD), and in ASCEND, the authors reported a 21% risk reduction for coronary death that just missed statistical significance (95% Confidence Interval = 0.61-1.02). Given that the study was not powered to detect such a difference, this finding should not be overlooked.

### **Vitamin D and Omega-3 Trial (VITAL)<sup>3</sup>**

Among other things, VITAL investigated whether taking daily vitamin D<sub>3</sub> (2000 IU) and/or 840 mg EPA+DHA (omega-3-acid ethyl esters) reduces the risk of major cardiovascular disease (CVD) events in people without CVD. These events were specifically defined as the composite of myocardial infarction (MI), stroke and CVD death. Subjects included 25,871 men and women.

While supplementation with omega-3s versus placebo did not result in a lower incidence of the major CVD events, the following results were statistically significant, providing further evidence that omega-3s do provide benefits for primary prevention:

- Total MI: 28% risk reduction (omega-3s: 145 events vs placebo: 200 events)
- Total CHD: 17% risk reduction (omega-3s: 308 events vs placebo: 370 events)
- Fatal MI: 50% risk reduction (omega-3s: 13 events vs placebo: 26 events)

The greatest reductions were demonstrated in those with low dietary fish intake and in African Americans. While this is noteworthy, scrutiny of the data is required to better understand these findings.

### **Reduction of Cardiovascular Events with EPA – Intervention Trial (REDUCE-IT)<sup>4</sup>**

REDUCE-IT evaluated, in 8,171 men and women, whether 3840 mg EPA (icosapent ethyl; Vascepa®), combined with a statin therapy, is superior to statin therapy alone, when used as a prevention in reducing long-term cardiovascular events in high-risk patients with mixed dyslipidemia.

The following results from REDUCE-IT were statistically significant when the treatment group was compared to placebo:

- Primary Endpoint Composite of the first occurrence of major adverse cardiovascular events (MACE), including cardiovascular death, nonfatal myocardial infarction (MI), nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization: 25% risk reduction
- Key Secondary Composite of CV death, MI, or stroke: 26% risk reduction

<sup>2</sup>[https://www.nejm.org/doi/pdf/10.1056/NEJMoa1804989?utm\\_source=Global+Organization+for+EPA+and+DHA+Omega-3s+List&utm\\_campaign=bbd4cdcdf5-EMAIL\\_CAMPAIGN\\_2018\\_08\\_27\\_09\\_45&utm\\_medium=email&utm\\_term=0\\_88a4a45d44-bbd4cdcdf5-407050929](https://www.nejm.org/doi/pdf/10.1056/NEJMoa1804989?utm_source=Global+Organization+for+EPA+and+DHA+Omega-3s+List&utm_campaign=bbd4cdcdf5-EMAIL_CAMPAIGN_2018_08_27_09_45&utm_medium=email&utm_term=0_88a4a45d44-bbd4cdcdf5-407050929)

<sup>3</sup>[https://www.nejm.org/doi/pdf/10.1056/NEJMoa1811403?utm\\_source=Global+Organization+for+EPA+and+DHA+Omega-3s+List&utm\\_campaign=ee00798d09-EMAIL\\_CAMPAIGN\\_2018\\_11\\_11\\_12\\_20&utm\\_medium=email&utm\\_term=0\\_88a4a45d44-ee00798d09-407050929](https://www.nejm.org/doi/pdf/10.1056/NEJMoa1811403?utm_source=Global+Organization+for+EPA+and+DHA+Omega-3s+List&utm_campaign=ee00798d09-EMAIL_CAMPAIGN_2018_11_11_12_20&utm_medium=email&utm_term=0_88a4a45d44-ee00798d09-407050929)

<sup>4</sup>[https://www.nejm.org/doi/pdf/10.1056/NEJMoa1812792?utm\\_source=Global+Organization+for+EPA+and+DHA+Omega-3s+List&utm\\_campaign=ee00798d09-EMAIL\\_CAMPAIGN\\_2018\\_11\\_11\\_12\\_20&utm\\_medium=email&utm\\_term=0\\_88a4a45d44-ee00798d09-407050929](https://www.nejm.org/doi/pdf/10.1056/NEJMoa1812792?utm_source=Global+Organization+for+EPA+and+DHA+Omega-3s+List&utm_campaign=ee00798d09-EMAIL_CAMPAIGN_2018_11_11_12_20&utm_medium=email&utm_term=0_88a4a45d44-ee00798d09-407050929)

- Cardiovascular Death or Nonfatal Myocardial Infarction: 25% risk reduction
- Fatal or Nonfatal Myocardial Infarction: 31% risk reduction
- Urgent or Emergent Revascularization: 35% risk reduction
- Cardiovascular Death: 20% risk reduction
- Hospitalization or Unstable Angina: 32% risk reduction
- Fatal or Nonfatal Stroke: 28% risk reduction
- Total Mortality, Nonfatal Myocardial Infarction or Nonfatal Stroke: 23% risk reduction

While Amarin, the sponsor of REDUCE-IT, claims that their product (EPA in the form of icosapent ethyl) is so different from other forms of EPA and other omega-3 formulations that the results of REDUCE-IT cannot be generalized to long-chain omega-3s, it is GOED's contention that the form of the fatty acid is more or less irrelevant when a product is consumed day after day.

Their opinion is also that, for the same reason, these results should not be combined with the results of existing research and meta-analyzed. It is certainly true that EPA and DHA have different biological activities, and probably different roles in cardiovascular prevention, and that more research is needed to better understand the effects of different combinations of these nutrients. It is also true that the protective effects reported for REDUCE-IT are larger than those observed in most other studies, but this can more easily be explained by differences in dosage than by the uniqueness of their product's formulation. Most clinical research on omega-3s has been conducted using around 840 mg of EPA+DHA per day, while REDUCE-IT used 3,840 mg, and it should come as no surprise that increasing dosage by a factor of 5 would lead to stronger outcomes. GOED believes that for cardiovascular protection the dosage and the consistency with which omega-3s are used are more important than the exact formulation. Moreover, and perhaps more importantly, the results of REDUCE-IT are consistent with the results of existing research.