Council for Responsible Nutrition
1828 L Street, NW, Suite 510 • Washington, DC 20036-5114
(202) 204-7700 • fax (202) 204-7701 • www.crnusa.org

October 04, 2017

VIA ELECTRONIC SUBMISSION

Cristian Cofré Sasso
Asesor Técnico
Departamento de Alimentos y Nutrición/División de Políticas Públicas Saludables y Promoción
Ministerio de Salud ; Chile
Teléfono: (+56 2) 2574 0610 | Anexo: 240610
cristian.cofre@minsal.cl / codex@achipia.gob.cl

Elena Smirnova
Coordinator of the CCNFSDU electronic working group on the review of the NRV-NCD for DHA and EPA for the Russian Federation
The Institute of Nutrition
Ustyinskiy proezd 2/14
Moscow 109240; Russia
smirnova@ion.ru / codex@ion.ru

German Secretariat of CCNFSDU (ccnfsdu@bmel.bund.de)
Secretariat, Codex Alimentarius Commission codex@fao.org)

Re: Call for Comments "Electronic working group on establishing NRV-NCD for EPA and DHA long chain OMEGA-3 fatty acids"

The Council for Responsible Nutrition (CRN) [1] is the leading trade association for the dietary supplement and nutritional products industry, representing manufacturers of dietary

[1] The Council for Responsible Nutrition (CRN), founded in 1973 and based in Washington, D.C., is the leading trade association representing dietary supplement and functional food manufacturers, marketers and ingredient suppliers. CRN companies produce a large portion of the functional food ingredients and dietary supplements marketed in the United States and globally. Our member companies manufacture popular national brands as well as the store brands marketed by major supermarkets, drug stores and discount chains. These products also include those marketed through natural food stores and mainstream direct selling companies. CRN represents more than 150 companies that manufacture dietary ingredients, dietary supplements and/or functional foods, or supply services to those suppliers and manufacturers. Our member companies are expected to comply with a host of federal and state regulations governing dietary supplements and food in the areas of manufacturing, marketing, quality control and safety. Our supplier and manufacturer member companies also agree to adhere to additional voluntary guidelines as well as to CRN's Code of Ethics. Learn more about us at www.crnusa.org.

ingredients and of national brand name and private label dietary supplements, many of which are multinational and already actively selling ingredients, finished products and services globally.

Previous CRN Comments

CRN respectfully submitted written comments (June, 2015) to the chairs of the electronic Working Group (eWG) regarding a series of ten questions, related specifically to the development of a NRV-NCD for Omega 3 fatty acids (DHA/EPA). We remain committed to this process and our response to Question 4 remains relevant and has not been dismissed.

Justification of NRV-NCD Do you agree that DHA and EPA intake is sufficiently important for public health, and that all information reviewed so far justifies the establishment of an NRV-NCD for food labeling purposes? If you disagree, please justify your answer supported by scientific references.	CRN and CRN Members agree that the intake of DHA and EPA is sufficiently important for public health, and that all information reviewed so far does justify the establishment of a NRV-NCD for food labeling purposes. Further, several robust and adequately controlled "health care cost analyses" have reported that intake of DHA and EPA can lead to demonstrable public health and personal health benefits, and the reduction of significant hospitalization events. Shanahan C.J & deLorimier, R. (2014) From Science to Finance-A Tool for Deriving Economic Implications from the Results of Dietary Supplement Clinical Studies. *Jrnl. Diet. Suppl.* DOI:10.3109/19390211.2014.952866.

Further CRN submitted a written response (August, 2015) to the second consultation and again applauded the scientifically-relevant process and conclusion by the chairs of the electronic Working Group. The CRN statement in support of the conclusion by the chairs of the electronic Working group is below.

"CRN is wholly in agreement with the text of the Second Consultation Document on an NRV-NCD for EPA+DHA and supports its submission for discussion at the 37th session (November 2015) of the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU).

In October, 2016, CRN submitted new information on a prospective multicenter, double-blind, placebo-controlled clinical trial (RCT) funded by the National institutes of Health, i.e., the OMEGA-REMODEL (Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction) trial to evaluate the hypothesis that 4 g/day of omega-3 fatty acids for 6 months post-acute myocardial infarction would provide cardia remodeling benefits, as determined by the primary study endpoint, change in left ventricular systolic volume index and secondary endpoints of change in noninfarct myocardial fibrosis, left ventricular ejection volume and infarct size (Heydari, et al., 2016[2]).

"The results published indicate that patients randomly assigned to the Omega-3 fatty acids treatment group had a significantly reduced left ventricular systolic volume index (-5.8%, P=0.17) and noninfarct myocardial fibrosis (-5.6%, P=0.026) in comparison to the placebo control. Further, patients treated with Omega-3 fatty acids also had a reduction in serum biomarkers of systemic and vascular inflammation and myocardial fibrosis. There were no adverse effects associate with the 4 g/day dose. This recent study provides important context to the importance of omega-3 fatty acids and a marker for cardiovascular disease."

World Health Organization (WHO) Nutrition Guidance Expert Advisory Group (NUGAG)

CRN appreciates the opportunity to review and comment on the abridged versions of the systematic reviews of the randomized controlled trials (RCTs), hereafter also referred to as Document 1 and the prospective cohort studies, hereafter also referred to as Document 2 from

[2] Heydari B, Abdullah S, Pottala JV, Shah R, Abbasi S, Mandry D, Francis SA, Lumish H, Ghoshhajra BB, Hoffmann U, Appelbaum E, Feng JH, Blankstein R, Steigner M, McConnell JP, Harris W, Antman EM, Jerosch-Herold M, Kwong RY. (2016).Effect of Omega-3 Acid Ethyl Esters on Left Ventricular Remodeling After Acute Myocardial Infarction: The OMEGA-REMODEL Randomized Clinical Trial. Circulation;134(5):378-91. doi: 10.1161/CIRCULATIONAHA.115.019949.

the World Health Organization (WHO) Nutrition Guidance Expert Advisory Group (NUGAG) Subgroup on Diet and Health.

After an extensive review of the current body of scientific literature, plus discussions with and comments from eWG member, the Global Organization for EPA and DHA Omega-3s (GOED) dated September 25, 2017, CRN is submitting our comments and answers to your questions.

Based on the breadth and global nature of research supporting the beneficial nature of regular intake of essential fatty acids, CRN supports the work of NUGAG in contributing to establishment of a NRV-NCD for EPA and DHA by providing their analyses of intake. Given the somewhat limited nature and method in reaching conclusions in Documents 1 and 2, there is a concern that inappropriate interpretation of the studies could hinder progress toward further focus on this important nutrient.

A study published in the journal, *Nutrition* documented that despite an increasing public understanding of the importance of regular intake of DHA and EPA, blood levels of omega-3 are significantly below optimum in both the US and in Germany.[3]

From the perspective of reaching overarching goals in making a substantive difference (improvement) in global public health initiatives, it is critical to focus on any (ANY) incremental steps that can avoid or decrease risk of serious disease/debility and add to healthy aging.

The global burden on non-communicable diseases, also termed chronic diseases, is overwhelming, and even risk decrements as inconsequential as one percent, can translate into

[3] Thuppal SV, et al. (2017) Nutrients Discrepancy between Knowledge and Perceptions of Dietary Omega-3 Fatty Acid Intake Compared with the Omega-3 Index. Nutrients 9(9). pii: E930. doi: 10.3390/nu9090930. (http://www.mdpi.com/2072-6643/9/9/930/htm).

millions of lives saved and millions of opportunities for a prolonged quality of life for those that would otherwise be afflicted.

Policy-makers and governmental / pan-national regulatory agencies must decide when sufficient scientific support has been developed to justify dietary and lifestyle public health recommendations. This principle was acknowledged by action on the part of the US Institute of Medicine (now the National Academy of Medicine) when it published an adequate intake level for omega-3s even though all aspects of tolerance and upper limits value establishment were not fully implemented[4].

CRN has been at the forefront of coalescing, moderating and publishing key scientific expertise in this arena. Last year in Hamburg, Germany, just prior to the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU), CRN (via CRN-International) held a scientific symposium on Optimal Nutrition, which has since been published in the *European Journal of Nutrition (EJoN)*[5]. The speakers and the conclusion made it clear that there are many dietary and lifestyle decisions that can and do affect one's quest for optimal nutrition, and that it is short-sighted and contrary to public health policy to not give credence and make necessary changes…or at least necessary recommendations. This year, CRN/CRN-I will hold a similar scientific symposium in Berlin at the forefront of CCNFSDU on "Healthy Aging".

As two prominent members of the US National Academy of Medicine, Food and Nutrition Board (FNB) have stated from the podium during key scientific discussions on this

[4] Institute of Medicine, Food and Nutrition Board. Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein, and amino acids (macronutrients). Washington, DC: National Academy Press; 2005.

[5] Shao AS, et al. (2017) Optimal nutrition and the ever‐changing dietary landscape: a conference report. Eur J Nutr DOI 10.1007/s00394-017-1460-9.

topic, "do NOT let the perfect be the enemy of the good (Voltaire)[6]. Better a diamond with a flaw than a pebble is another way to state the irrational pursuit of perfection and the sacrifice of current health opportunities in an age of ever-increasing chronic disease and debility.

Several years ago, the CRN/CRN-I scientific symposium focused on a process whereby a bioactive ingredient could and should be considered for NRV/DRI review and progression. All of the international speakers were in agreement and the subsequent *EJoN* publication[7] put into the scientific literature, a well-discussed, well-vetted and well-accepted list of criteria that when met, were sufficient such that public policy could go forward in setting a NRV-NCD (or in the US, a DRI) for a bioactive ingredient. Those criteria have been met for EPA+DHA and there is NO scientific reason, much less common-sense reason to avoid making the appropriate recommendation for CCNFSDU to go forward.

Document 1 - Systematic review and meta-analysis of RCTS

Q1.1 Do you believe that Document 1 represents/summarizes relevant convincing/generally accepted scientific evidence or the comparable level of evidence under the GRADE classification for the relationship between EPA/DHA and noncommunicable disease risk, as required for the selection of nutrients by 3.2.2.1 of General Principles for Establishing NRVs?

NO

Q1.2 Do you believe that Document 1 represents/summarizes relevant and peer-reviewed scientific evidence for quantitative reference values for daily intake that is required in order to determine an NRV-NCD that is applicable to the general population, according to 3.2.2.2 of General Principles for Establishing NRVs?

NO

[6] *Le mieux est l'ennemi du bien***.** Voltaire, Dictionnaire Philosophique.
[7] Lupton J, et al. (2014) Exploring the benefits and challenges of establishing a DRI-like process for bioactives. Eur J Nutr. 2014 Apr;53 Suppl 1:1-9. doi: 10.1007/s00394-014-0666-3 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3991826/pdf/394_2014_Article_666.pdf.

Q1.3 Do you believe that Document 1 (section Coronary Heart Disease deaths, pages 48-54) presents evidence that sufficiently characterizes the relationship between EPA/DHA intake and the reduction of risk of CHD mortality/fatal CHD events, the health outcome selected for establishing the NRV-NCD?

NO

Q1.4 Authors of Document 1 have run sensitivity analysis excluding certain RCTs from the scope of the review. Do you find results of the sensitivity analysis which excluded RCTs reporting cardiac deaths only (figure 4.16 on page 50) relevant to establishing the NRV-NCD for EPA/DHA associated with CHD mortality?

NO

Q1.5 Figure 4.18 on page 52 depicts results of the sensitivity analysis which grouped studies based on the summary risk of bias. Do you find results of the sensitivity analysis which grouped RCT studies according to their summary risk of bias relevant to establishing the NRV-NCD for EPA/DHA associated with CHD mortality?

NO

Q1.6 Several RCT studies selected for review in the CHD mortality section of Document 1 were based on a comparison of EPA/DHA intake with intake of monounsaturated fatty acids (MUFA). Considering that there was convincing evidence that MUFA lowered levels of heart health biomarkers, comparing effects of EPA/DHA with MUFA intakes might not be entirely suitable for establishing an NRV-NCD. Do you agree that for the purpose of establishing the NRV-NCD the sensitivity analysis may require exclusion of all studies that compared EPA/DHA intake with MUFA intake?

NO

Document 2 - Systematic review and meta-analysis of prospective cohort studies

Q2.1 Do you believe that Document 2 represents/summarizes relevant convincing/generally accepted scientific evidence or the comparable level of evidence under the GRADE classification for the relationship between EPA/DHA and noncommunicable disease risk relationship, as required for the selection of nutrients by 3.2.2.1 of General Principles for Establishing NRVs?

NO

Q2.2 Do you believe that Document 2 represents/summarizes relevant and peer-reviewed scientific evidence for quantitative reference values for daily intake that is required in order to

determine an NRV-NCD that is applicable to the general population, according to 3.2.2.2 of General Principles for Establishing NRVs?

NO

Q2.3 Do you believe that Document 2 presents evidence that sufficiently characterizes the relationship between long chain n-3 PUFA intake and the reduction of risk of CHD mortality/fatal CHD events, the health outcome selected for establishing the NRV-NCD?

YES

Q2.4 Do you agree that results reviewed in Document 2 for total long chain n-3 PUFAs could be accepted as representative for associations of EPA/DHA with various health outcomes studied including the CHD mortality?

YES

Further, although not every omega 3 fatty acid study exhibits strong causal relationships, in fact a number of studies do suggest such a causal relationship. Please refer to Szolstak-Wegierek, et al. "The role of dietary fats for preventing cardiovascular disease, a review[8]" or the 2015 *JCN* article titled "Replacement of saturated with unsaturated fats had no impact on vascular function but beneficial effects on lipid biomarkers, E-selectin, and blood pressure: Results from the randomized, controlled Dietary Intervention and Vascular Function (DIVAS) study[9]" where certain correlations exist, but it would be difficult to identify a specific level, or even range of levels, at which below, there is no influence and, at which above, there is a consistent significant influence. When you add in the additional risk of bias analysis, cited in the NUGAG report, some type of positive relationship between PUFAs and heart health exists,

[8] Szostak-Wegierek, et al (2013). The role of dietary fats for preventing cardiovascular disease. A review Rocz Panstw Zakl Hig. 2013;64(4):263-9.

[9] Vafeiadou K, et al. (2015). Replacement of saturated with unsaturated fats had no impact on vascular function but beneficial effects on lipid biomarkers, E-selectin, and blood pressure: results from the randomized, controlled Dietary Intervention and VAScular function (DIVAS) study. Am J Clin Nutr. 2015 Jul;102(1):40-8. doi: 10.3945/ajcn.114.097089. Epub 2015 May 27.

but the data may be less convincing when looking to set a specific NRV-NCD or establishing specific health outcomes, but that does not mean one should avoid making realistic public health policy decisions.

Nothing has been proposed in the scientific literature and/or amongst national regulatory bodies that in any way changes the conclusion of CRN, as echoed by the chairs of the electronic Working Group. In fact the current recommendations set by the European Food Safety Authority (EFSA) identify a 250 mg intake of EPA and DHA per day for the general adult population with a maximum tolerated dose of 5 g per day. CRN is in agreement with EFSA on their analysis, conclusion and recommendation.

Q10	**Proposed NRV-NCD value** If you replied affirmatively to question 9, what Reference Value amount for EPA and DHA would you propose, expecting the mentioned health benefits? Please justify your answer.	CRN and CRN Members support the establishment of a single internationally harmonized NRV-NCD for EPA and DHA combined for the general population for labeling purposes in an amount between 250-500 mg/day.

Should the eWG have further questions that CRN could address, please do not hesitate contacting me at your earliest convenience. CRN awaits a review of subsequent consultation papers and eWG recommendations on this important issue.

Respectfully submitted,

James C Griffiths, Ph.D., DABT, FSB, CFS
Diplomate, American Board of Toxicology
Fellow, Royal Society of Biology (U.K.)
Certified Food Scientist