CODEX ALIMENTARIUS COMMISSION

Food and Agriculture Organization of the United Nations

World Health Organization

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JOINT FAO/WHO FOOD STANDARDS PROGRAMME

CODEX COMMITTEE ON NUTRITION AND FOODS FOR SPECIAL DIETARY USES

Thirty-sixth Session
Kuta, Bali - Indonesia
24 – 28 November 2014

PROPOSALS FOR NEW WORK

Comments from Austria, Switzerland and IADSA

AUSTRIA

Proposal for an extension of the method recommendation in CODEX STAN 118 – 1979 (CODEX STANDARD FOR FOODS FOR SPECIAL DIETARY USE FOR PERSONS INTOLERANT TO GLUTEN) with a method that accurately detects the toxic fraction in gluten harmful for individuals intolerant to gluten: the ELISA G12 method

In 2008, the Codex Alimentarius Commission revised Codex Standard 118-1979[1].
The important changes are found in section 5 “Methods of analysis and sampling”, subsection 5.1 “General outline of the methods”. Looking at these method criteria, it is clearly stated that all appropriate immunological methods meeting these requirements are acceptable. The Enzyme-linked Immunoassay (ELISA) Method using the G12 antibody is meeting all of the listed criteria:

> *1. The **quantitative determination** of gluten in foods and ingredients **shall be based on an immunologic method** or other method providing at least equal sensitivity and specificity.*
>
> *2. The **antibody used should react with the cereal protein fractions that are toxic for persons intolerant to gluten** and should not cross-react with other cereal proteins or other constituents of the foods or ingredients.*

The **G12 antibody** was raised against the so called 33-mer, which was identified as the primary initiator of the inflammatory response to gluten in Celiac Sprue patients[2].

> *3. Methods used for determination should be **validated** and **calibrated against a certified reference material**, if available.*
>
> *4. The **detection limit** has to be appropriate according to the state of the art and the technical standard. **It should be 10 mg gluten/kg or below**.*

An ELISA Method using this antibody (AgraQuant® Gluten G12) was recently approved as ***AACC international method 38-52.01*** as well as ***AOAC official method of analysis 2014.03*** based on an international collaborative study[3,4]. The standards of this extensively validated G12 ELISA method are calibrated against the WGPAT (Working Group on Prolamin Analysis and Toxicity) gliadin standard material, which is the most recognized reference material available in the industry (there is no official reference material for Gluten or any other allergen available). The limit of detection (**LOD**) stated in the collaborative study was calculated according to recommendations from AOAC and was **4.3 mg/kg Gluten**[4,5,6], which is clearly meeting the CODEX requirements.

> *5. The **qualitative analysis** that indicates the presence of gluten shall be **based on relevant methods** (e.g. ELISA-based methods, DNA methods).*

One such example would be a lateral flow device incorporating the G12 antibody.

Comparability of the existing recommended ELISA R5 Mendez method and the G12 antibody based ELISA method

The Austrian agency for health and food safety (AGES) initiated a study to investigate the comparability of the official CODEX Alimentarius type 1 method (R5 Mendez method) and the Gluten G12 ELISA method. There a total of 60 food routine samples, all labelled gluten free but with a content above LOQ of the type 1 method (R5 ELISA, LOQ = 2,5 mg/kg Gliadin), were re-assayed in parallel. To eliminate side-errors no commercial kit extraction procedure was used. Instead an in-house modified extraction method was applied that combines the ethanol and cocktail extraction. Summarizing it can be said that results obtained with the G12 antibody ELISA assay are comparable to the official R5 method. Real life samples results by the official R5 methods could be confirmed with the G12 method and therefore it is a suitable method[7].

Conclusion statement

Since this ELISA G12 method fulfills all the criteria stated in 5.1 in the Codex Standard 118-1979, and is supported by elaborate interlaboratory validation data and international approvals we strongly emphasize considering the inclusion of the G12 ELISA method or any other method incorporating an antibody detecting the 33-mer into Codex Standard 118-1979.

This inclusion could only be beneficial for the safety of celiacs, driving technological development further into the direction targeting the immunotoxic peptide that plays the pivotal role in the pathogenesis of coeliac disease rather than measuring a cross reactivity to this crucial peptide.

Furthermore it could be shown that the ELISA G12 method provides results comparable to the Codex Alimentarius type 1 R5 ELISA method as shown in the study by the Austrian agency of health and food safety.

Literature

1 Codex Alimentarius Commission. Codex Standard 118-1979 (rev. 2008), Foods for special dietary use for persons intolerant to gluten Codex Alimentarius FAO/WHO Rome (2008)

2 Shan L et al Structural Basis for Gluten Intolerance in Celiac Sprue *Science* **297**: 2275-2279 (2002)

3 Don C, Halbmayr-Jech E, Rogers A, Koehler P AACCI approved methods technical committee report: Collaborative Study on the Immunochemical Quantitation of Intact Gluten in Rice Flour and Rice-Based products by G12 Sandwich ELISA *Cereal Foods World* **59**: 187-193(2014)

4 AOAC Official Method 2014.03: Gluten in Rice Flour and Rice-Based Food Products G12 sandwich ELISA, First Action 2014

5 AOAC International, Appendix D: Guideline for collaborative study procedures to validate

characteristics of a method of analysis. In: AOAC Official methods of analysis (2002)

6 Abbott M, Hayward S, Ross W, Godefroy SB, Ulberth F, van Hengel AJ, Roberts J, Akiyama H, Popping B, Yeung JM, Wehling P, Taylor SL, Poms RE, Delahaut P Validation procedures for quantitative food allergen ELISA methods: community guidance and best practices. *J. AOAC Int.* **93**: 442-450 (2010)

Attachments

7 Presentation of Rupert Hochegger (AGES) at the GlutenFree 2013

SWITZERLAND

PROJECT DOCUMENT

PROPOSAL
FOR INCLUSION OF ZINC CITRATES IN THE
CODEX ALIMENTARIUS GUIDELINE CAC/GL 10 – 1979
ADVISORY LISTS OF NUTRIENT COMPOUNDS FOR USE IN FOODS FOR SPECIAL DIETARY USES INTENDED FOR INFANTS AND YOUNG CHILDREN

PURPOSE AND SCOPE OF THE PROPOSED WORK

The lists of the Guideline CAC/GL 10 - 1979 include nutrient compounds, which may be used for nutritional purposes in foods for special dietary uses intended for infants and young children. They have to be used in accordance with certain other criteria for their use stipulated in the respective standards. In addition, the sources from which the nutrient compound is produced may exclude the use of specific substances where religious or other specific dietary restrictions apply. As noted in the respective standards, their use may either be essential or optional.
The Guideline CAC/GL 10 – 1979 lists several zinc compounds suitable for food fortification. The main purpose of this proposed work is to add a freely available biologically highly available and safe source of zinc to the present listings.

The guideline requires certain criteria met according to Art. 2 of CAC/GL 10 1979 for incorporation in the listing:

- Safety for infants and young children
- Biological availability
- Adequate purity
- Stability in foods
- Criteria for the demonstration of the abovementioned items by generally accepted scientific criteria

Zinc citrate was already proposed for inclusion in CAC/GL 10 1979 in 2000, but was not considered due to the fact that back then, no specification or purity was available. In the meantime, an USP specification is available.

Thus, zinc citrate now complies to all of these requirements and should be included in CAC/GL 10- 1979.

RELEVANCE

Zinc supplementation is highly desirable in foods for infants and young children:

- Infant formula may act as a replacement for breast milk, thus it has to provide all essential nutrients and zinc is one of this nutrients.
- There are several good reasons to suspect that zinc deficiency is common, especially in infants and children (1).
- Several randomized control trials have demonstrated that stunted children, and/or those with low plasma zinc, respond positively to zinc supplementation, a finding that suggests that zinc deficiency was a limiting factor in their growth, however zinc is only one of of several possible causes of stunt growth (1).

JUSTIFICATION OF THE PROPOSAL

Zinc citrate has some advantages over other sources of zinc. It has a high zinc content and has better sensory properties than other zinc compounds, especially when ingested in higher amounts. It is stable under common processing and storage conditions of food.

Several sources of zinc are listed in the Guideline CAC/GL 10 – 1979 and citrate as the anion is listed for most metal sources like iron, magnesium, sodium, potassium, copper and manganese.

Examples of countries specifically approving fortification with zinc citrate, including infant and follow-on food are Switzerland and the EU. Switzerland approves zinc citrate for use in infant formulae and follow-on formulae, processed cereal-based foods and baby foods for infants and young children, dietary supplements (2) and for food fortification (3). In the EU zinc citrate is approved for these applications, too, and for use in foods for special dietary uses (4 - 8). While zinc citrate is not specifically listed as a nutrient in the USA the USP contains a respective monograph (9). Zinc citrate is also self-affirmed as GRAS (Generally Recognized As Safe).

SAFETY

Citric acid

Citric acid is a constituent of many fruits, approved for many uses following good manufacturing practice or the quantum satis principle in Switzerland and the EU (10,11) and GRAS in the USA (12)

The safety of citric acid was examined by the United Nations Environment Program (UNEP) Screening Information Data Set (SIDS) in 2001. This group reviewed existing data on citric acid and found the citric acid has a low oral toxicity in rats and mice (LD_{50} 3 - 12 mg/kg bw and 5.4 mg/kg bw respectively. No adverse effects should occur at fortification with trace levels. The No Observed Adverse Effect Level for repeated toxicity was 1.200 mg/kg bw and for reproductive toxicity 2.500 mg/kg bw.

Zinc

Zinc is involved in metabolic pathways as a constituent of enzymes. It is therefore essential for growth and development testicular maturation, neurological function,
wound healing and immunocompetence and is present in all tissues of the human body.

Symptoms of mild/marginal zinc deficiency include delayed wound healing, impaired resistance to infection and reduced growth rate (14).

The former Scientific Committee on Food of the EU (SCF) summarized data which indicate a NOAEL for zinc of around 50 mg/day and recommends an Upper Limit of zinc of 25 mg/day. Converting this into the smaller body weight of infants and young children this would correspond to 4 mg for 0 – 6 month old infants and 12 mg for 8 – 12 year old children. The SCF set the following tolerable upper levels per day: 7 mg for age 1 – 3 , 10 mg for age 4 – 6, 13 mg for age 7 – 10 and 18 mg for age 11 – 14 (14). The upper safe levels per day in the USA are 4 mg for birth to 6 months, 5 mg for 7 - 12 months,7 mg for age 1 - 3, 12 mg for age 4 – 8 and 23 mg for age 9 – 13 (15).

The former Scientific Committee on Food of the EU refers to estimated average requirements of 7.3 mg/day for males and 5.5 mg/day for females (14). The recommended daily intakes in the USA are 2 mg for birth to 6 months, 3 mg for 7 months to age 3, 5 mg for age 4 – 8 and 8 mg for age 9 – 13 (15).

Applicable national legislation often limits fortification to levels far below the tolerable upper limits. Switzerland and the EU equally require a zinc level of 0.5 – 1.5 mg per 100 kcal in infant formulae and follow-on formulae and limit the level to not more than 2 mg per 100 kcal in processed cereal-based foods and baby foods for infants and young children (2, 4, 5). The USA require a minimum of 0.5 mg per 100 kcal (16).

BIOAVAILABILITY

Absorption of zinc takes place in the small intestine and appears to be a carrier-mediated transport process which is not saturated under normal physiological conditions. Absorption of dietary zinc ranges from 15 to 60%. At very low zinc intakes, absorption can increase to between 59 and 84%. Most of the absorbed zinc is excreted in the bile and eventually lost in the faeces (14).

The bioavailability of ingested zinc depends on several factors like type of the salt ingested, amount in the diet and simultaneous ingestion of other substances that promote or interfere with zinc absorption (14).

A study comparing different sources of zinc was carried out in 15 adults of 18 – 45 years of age in a randomised double-masked 3-way crossover design. They received a a dose of 10 mg in a supplement. Zinc absorption was measured by a double-isotope tracer method using ^{67}Zn and ^{70}Zn. The study showed that absorption from zinc citrate is comparable to zinc gluconate but higher than for zinc oxide with median values of 61.3 %, 60.9 % and 49.9 %, respectively (17).

SPECIFICATIONS AND PURITY CRITERIA

Two alternatives are commercially available for zinc supplementation: zinc citrate dihydrate and zinc citrate trihydrate.

Purity standards are set for zinc citrate dihydrate in the US Pharmacopoeia (9):

Chemical Formula	$C_{12}H_{10}O_{14}Zn_3 \cdot 2H_2O$
Molecular mass	610.36
Chemical name	2-Hydroxy-1.2.3-propanetricarboxylic acid zinc salt, dihydrate

Synonym	Zinc citrate dihydrate
CAS number	5990-32-9
Identification	
Zinc	Meets the requirements
Citrate	Meets the requirements
Assay	Not less than 31.3 % on the dried basis
Arsenic:	Not more than 3 µg/g
Cadmium:	Not more than 5 µg/g
Lead:	Not more than 10 µg/g
Loss on drying	Not more than 1.0%

Similar standards apply for zinc citrate trihydrate supplied for nutritional purposes (18):

Chemical formula	$(C_6H_5O_7)_2\ Zn_3 \cdot 3\ H_2O$
Molecular mass	628.42
Chemical name	2-Hydroxy-1.2.3-propanetricarboxylic acid zinc salt, trihydrate
Synonym	Zinc citrate trihydrate
CAS number	546-46-3 (anhydrous)
Identification	Meets the requirements
Assay	30.9 – 33.0 % on the dried basis (as Zn)
Arsenic:	Not more than 2 µg/g
Cadmium:	Not more than 1 µg/g
Lead:	Not more than 5 µg/g
Mercury	Not more than 1 µg/g
Loss on drying	Not more than 1.0%

ASSESSMENT AGAINST THE CRITERIA FOR THE ESTABLISHMENT OF WORK
Priorities

As other sources of zinc and other citrates are listed in the Guideline CA /GL 10 – 1979, a decision on the proposed action concerning the zinc citrate with good bioavailability could be possible on the data and information submitted in this proposal and would not necessarily delay the priorities of the work program of the relevant Codex Standards.

Relevance to the codex strategic objectives

While fortification of essential nutrients is in the remit of Codex Alimentarius, additional and improved alternative nutrients with improved bioavailability should be considered and listed for the Codex Guidelines and therefore be applicable for the respective standards.

Identification of any requirement for and availability of expert
Scientific advice

Non foreseen.

PROPOSED TIME-LINE FOR COMPLETION OF THE NEW WORK SUBJECT TO APPROVAL

2014: Discussion of the proposal at the 36th CCNFSDU meeting with the request for inclusion of zinc citrate into Guideline CAC/GL – 1979.
2015: Acceptance of the proposal and inclusion of zinc citrate in the Guideline.

REFERENCES

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(3) Verordnung des EDI ueber den Zusatz essenzieller oder physiologisch nuetzlicher Stoffe zu Lebensmitteln (Regulation of the EDI on addition of essential or physiologically useful substances to food) http://www.admin.ch/opc/de/classified-compilation/20050169/index.html

(4) Commission Directive 2006/141/EC on infant formulae and follow-on formulae http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1407326654183&uri=CELEX:02006L0141-20130918

(5) Commission Directive 2006/125/EC on processed cereal-based foods and baby foods for infants and young children http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1407327137687&uri=CELEX:32006L0125

(6) Commission Directive 2002/46/EC on the approximation of the laws of the Member States relating to food supplements http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1407327335374&uri=CELEX:02002L0046-20140228

(7) Commission Regulation (EC) No 1925/2006 on the addition of vitamins and minerals and of certain other substances to foods http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1407327638952&uri=CELEX:02006R1925-20140228

(8) Commission Regulation (EC) No 953/2009 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses http://eur-lex.europa.eu/legal-content/EN/TXT/?qid=1407328306370&uri=CELEX:02009R0953-20111205

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(12) US Code of Federal Regulations 21§184.1033 http://www.gpo.gov/fdsys/pkg/CFR-2013-title21-vol3/pdf/CFR-2013-title21-vol3-sec184-1033.pdf

(13) SIDS Initial Assessment Report – Citric Acid http://www.inchem.org/documents/sids/sids/77929.pdf

(14) Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Zinc http://ec.europa.eu/food/fs/sc/scf/out177_en.pdf

(15) US National Institutes of Health, Office of Dietary Supplements: Zinc – Fact Sheet for Health Professionals http://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/

(16) US Code of Federal Regulations 21§107.100 http://www.gpo.gov/fdsys/pkg/CFR-2013-title21-vol2/pdf/CFR-2013-title21-vol2-sec107-100.pdf

(17) R. Wegmueller et al.: Zinc Absorption by Young Adults from Supplemental Zinc Citrate Is Comparable with That from Zinc Gluconate and Higher than from Zinc Oxide. J. Nutrition 144 (2), 133 – 136 (2014) 10.3945/jn.113.181487; http://jn.nutrition.org/content/144/2/132.full

(18) Manufacturer´s specification sheet

IADSA - INTERNATIONAL ALLIANCE OF DIETARY/FOOD SUPPLEMENT ASSOCIATIONS

Proposal for New Work on the establishment of a Codex Nutrient Reference Value (NRV) for eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) long chain omega-3 fatty acids by the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU)

1. Introduction

The purpose of the proposed new work is to establish a Codex Nutrient Reference Value (NRV) for omega-3 fatty acids based on combined EPA and DHA intended for the general population. The proposed new work is relevant to the current work of the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) on setting NRVs for labelling purposes for essential nutrients, i.e. NRV-Requirements (NRV-Rs) and for those nutrients associated with risk of diet-related Non-Communicable Diseases (NRV-NCDs) in the *Codex Guidelines on Nutrition Labelling (CAC/GL 2-1985).*

This discussion paper intends to present a thorough review on this subject to facilitate consideration and discussion by the CCNFSDU, which includes relevant scientific evidence for the diet and health relationship, the public health importance and the scientific evidence for a quantitative reference value for daily intake of omega-3 fatty acids based on DHA and EPA.

A tabulation of global recommendations for EPA and DHA, as shown in Appendix I of this paper and which is compiled by the Global Organisation for EPA and DHA Omega-3 (GOED), has consolidated the daily nutrient intake values from the Food and Agriculture Organisation (FAO), the World Health Organisation (WHO) and other Recognised Authoritative Scientific Bodies (RASBs) supported by a competent national and/or regional authority. These bodies provide independent, scientific and authoritative advice on daily intake reference values (DIRVs) through primary evaluation of the scientific evidence. These studies have provided strong justification for the establishment of an NRV for these omega-3 fatty acids for the health and wellbeing of the general population, and they should serve as the basis for the establishment of the proposed new NRV.

It is believed that the establishment of a Codex NRV for omega-3 fatty acids based on combined EPA and DHA will help inform nutrition policy decisions at international and national levels, and reduce consumer uncertainty about a dietary target for these omega-3 fatty acids through nutrition labelling.

A Project Document, which provides consideration on the Codex general principles and criteria for setting up NRVs, is presented in Appendix II of this paper.

2. The evidence base

The evidence base regarding the biological effects of EPA and DHA has progressed significantly over the past decade, which has led to a number of organisations and expert groups around the world to issue recommendations (Harris *et al*., 2009; Flock *et al*., 2013; Kris-Etherton *et al*., 2014). Omega-3 polyunsaturated fatty acids (n-3 PUFAs), specifically EPA and DHA, modulate both metabolic and immune processes and confer health benefits in areas of cardiovascular disease (CVD) and neurodevelopment. The effects of EPA and DHA in healthy adults, relating to primary prevention of CVD, are considered to be the most relevant for establishing an NRV (Harris *et al*., 2009; Flock *et al*., 2013). These cardiovascular protective benefits of EPA and DHA on CVD risk factors and the biological mechanisms are multifaceted and clearly highlight the importance of establishing a Codex NRV that is appropriate to meet the needs of the healthy general population, not individuals with disease. With respect to cardiovascular diseases, prospective epidemiological and dietary intervention studies indicate that oily fish consumption or dietary n-3 PUFA supplements (equivalent to a range of 250 to 500 mg of EPA and DHA daily) decrease the risk of mortality from CHD and sudden cardiac death (Flock *et al*., 2013). As part of a systematic analysis for the Global Burden of Disease Study 2010 and based on an updated meta-analysis on the relation between intake of seafood omega-3 fatty acids and the risk of coronary heart disease (CHD), the global burden of a diet low in seafood (rich source of EPA and DHA) was 1.1% of global disability-adjusted life years (DALYs; 95% CI 0.8–1.5), with 22% of ischaemic heart disease DALYs attributable to low seafood intake (Engell *et al*., 2013; Lim *et al*., 2012). On the basis of the available data, the European Food Safety Authority (EFSA, 2010) concluded that an intake of 250 mg per day of EPA and DHA appears to be sufficient for primary prevention in healthy subjects, and this RASB proposed setting an Adequate Intake (AI) of 250 mg/day for adults based on cardiovascular considerations. EFSA also stated that, with the evidence currently available, it is not possible to define an age-specific quantitative estimate of an adequate dietary intake for EPA and DHA for children aged two to 18 years. It advised that dietary advice for children should be consistent with advice for the adult population, i.e. one to two fatty fish meals per week or about 250 mg EPA and DHA per day. It is widely accepted that long-chain polyunsaturated fatty acids are also important for the growth and development of infants. Sufficient DHA during pregnancy and after birth is essential because it is the predominant structural fatty acid in the central nervous system and retina, and its availability is crucial for brain development (Kris-Etherton *et al*., 2009). As a result, recommendations have been made for pregnant and lactating women. For example, EFSA recommends that women consume ≥ 250 mg/day of EPA and DHA plus 100–200 mg of preformed DHA. For older infants, EFSA considers that DHA intakes of 50–100 mg/day are effective for visual function and are adequate for the period of complementary feeding with respect to normal brain development (EFSA, 2010).

It should be noted that, from the numerous epidemiological studies showing an inverse relationship between EPA and DHA intake and CVD outcomes, a level of 250 mg/day was the lowest level that significantly reduced the risk of cardiovascular events (Flock *et al*., 2013). However, the greatest reduction in risk of CHD mortality (roughly 37%) was associated with intakes of around 566 mg/day. Evidence from primary and secondary prevention studies of CVD has also provided data suggesting that a total of 250 mg/day EPA and DHA reduces mortality from CHD or sudden death in persons with and without CVD (Flock *et al*., 2013). Although further human intervention studies could unravel some of the inconsistencies observed between the epidemiological evidence and some results from human intervention studies, there is already a large body of convincing evidence that supports CVD benefits related to increased intakes of EPA and DHA, and

compelling reasons for establishing an NRV (Kris-Etherton *et al*., 2009; Harris *et al*., 2009; Flock *et al*., 2013; Grieger *et al*., 2013). On the basis of the totality of the available scientific evidence, it is likely that potential healthcare cost savings and economic benefits could be achieved not only for the health and wellbeing of the general population, but also for vulnerable, higher-risk population groups, which are likely to be the greatest contributors to total healthcare costs in countries around the world (Council for Responsible Nutrition, USA, 2013; Complementary Healthcare Council of Australia 2012; Lim *et al.* 2012). Although the optimal amount of n-3 PUFA remains to be resolved, it is becoming clear that, in humans, the endogenous synthesis of EPA and DHA (carbon 20 and 22, respectively) from alpha linolenic acid (ALA), the shortest n-3 PUFA (an 18-carbon fatty acid) is minimal (Flock *et al*., 2013), and that tissue levels are determined largely by the direct consumption of EPA and DHA. These nutrients have very specific metabolic functions that are not duplicated by other fatty acids. Indeed, EPA and DHA could be viewed as conditionally essential fatty acids.

In addition to the benefits for cardiovascular health, EPA and DHA have also been shown to affect cognitive functions and visual development beneficially (Harris *et al*., 2009; Flock *et al*.). The evidence of beneficial effects of EPA and DHA on age-related cognitive decline is emerging and is not yet considered sufficient to support an intake level different from that needed for CVD benefits. Nevertheless, the implications for normal neurodevelopmental benefits and modulation of losses of cognitive function in ageing populations are significant for public health.

3. Sources of EPA and DHA

Both EPA and DHA are present in seafood and all fish oil supplements, although the ratio between the two can differ, with fish typically having more DHA and supplements more EPA (Harris *et al*., 2009). Virtually all observational studies and human intervention studies on disease outcomes have evaluated the effects of EPA and DHA combined. The main cardiovascular effect of EPA and DHA to reduce risk of fatal heart attacks is likely to result mainly from a reduction of cardiac arrhythmias, as well as other beneficial outcomes (Harris *et al*., 2009). The current evidence, however, does not permit strong conclusions as to whether EPA or DHA, or a specific ratio of the two, is the most beneficial. Based on this uncertainty, both these fatty acids are recommended to be consumed in ratios between 1:2 and 2:1 in order to maximise cardiac health (Harris *et al*., 2009).

Although fish is a uniquely rich source of n-3 PUFAs, other natural sources are human milk, cultivated marine algae, marine mammals and krill. Dietary sources of the n-3 PUFAs and ALA also include canola and soybean oils, walnuts and flaxseed oil, the latter being one of the most concentrated sources of ALA known. Terrestrial meats (beef, pork, mutton and poultry), particularly from grass-fed livestock, can contribute significant amounts of n-3 PUFAs, primarily in the form of ALA and decosapentaenoic acid (DPA). However, oils found naturally in fish are the richest dietary sources of EPA and DHA.

As previously stated, recommendations for n-3 PUFA intake have been put forward by several organisations around the world. Most focus on primary prevention of CHD in the general healthy population, with recommendations to increase consumption of fish, particularly oily fish, whereas other focus on the actual nutrients, EPA and DHA. Whether the recommendation is for fish or for EPA and DHA, the resulting amounts of EPA and DHA typically fall between 200 and 600 mg/day. Generally, nutritionists recommend a food-based approach for achieving adequacy and for reduction of risk of diseases. However, in some cases, foods with added nutrients or food (dietary) supplements are needed to meet nutritional needs. Certainly, for vegans and for individuals who are allergic or cannot eat fish, or choose not to include fish in their diet, dietary strategies for achieving the recommendations include the use of fortified foods and food supplements. Specialized fish oil concentrates with different ratios of EPA and DHA are now available commercially. The ratio of EPA and DHA is different in fish and fish oil supplements, and human studies have shown that those people who either ate fish with relatively more DHA relative to EPA, or those who consumed fish oil supplements with relatively more EPA than DHA, had similar reductions in cardiac death by 33% and all-cause mortality by 29% (Kris-Etherton *et al*., 2009). Although it is not clear whether both fatty acids confer comparable cardiac protective effects, combined target recommendations for EPA and DHA have been issued by most authoritative bodies based on the available scientific data. The amount of EPA and DHA together appears to be the most pragmatic and physiologically sensible way to establish an NRV taking into account the large public health benefits to be expected. Interestingly, although there is potential to include an appropriate number of seafoods into a usual weekly diet, these recommendations usually produce a poor result with respect to achieving the target amount of EPA and DHA. Theoretical dietary modelling of Australian seafood species shows that significant numbers of adults, mostly men and all older adults, would have difficulty in achieving the EPA and DHA targets when choosing a combination of higher and lower fat seafood. The choice of lower fat seafood would not enable any older adult to meet the dietary recommendations. Hence, additional dietary strategies, including the use of fish oil supplements, would have to be considered to achieve the suggested dietary target (Grieger *et al*., 2013).

An important question is whether measures to increase seafood and fish oil supplements is sustainable globally, and whether suppliers would be able to meet increased demands. Fish farms, aquacultures, the use of non-marine sources including specific strains of algae, products of biotechnology and recent developments of innovative EPA and DHA products have all helped to provide alternative sources of n-3 PUFAs (Harris *et al.*, 2009).

4. Dietary intake assessment and n-3 nutritional status

The bulk of the scientific evidence is now pointing towards not so much optimal ratios of dietary n-3 and n-6 fatty acids, but rather towards the absolute intakes of specific n-3 and n-6 PUFAs that are associated with many different endpoints and health outcomes, such as CHD, mental health or immune/inflammatory responses (Deckelbaum and Calder, 2010). As previously shown, the evidence related to intake amounts for n-3 PUFAs are best defined for CVD. What is abundantly clear is the total disconnect regarding the amounts of seafood and EPA and DHA that are needed in order to meet dietary recommendations and what is actually consumed (Grieger *et al.*, 2013). Most populations are not meeting current recommendations for omega-3 fatty acid intakes.

Reliable and valid dietary intake assessments are crucial in determining DIRVs (Flock *et al.*, 2013). This poses a challenge for all nutrients, including EPA and DHA. The amounts, duration of intake, sources of EPA and DHA, dietary and lifestyle factors, choice of healthy individuals versus patients, inconsistencies in the design, execution and interpretation of studies all contribute to the challenge of establishing DIRVs and NRVs. Much more information is needed about the endogenous production of EPA and DHA in vegans and vegetarians, interindividual variability in responses to EPA and DHA, different responses in relation to age, sex, weight, race, specific genotypes and overall health status. Up-to-date food composition databases are also important for assessing n-3 PUFA intake, and the limitations of food intake records have to be taken into account. For example, EFSA (2012) selected references in order to obtain data on intake distributions in European countries. Mean daily intakes for adults of EPA from food only ranged between 50 and 150 mg/day and median daily intakes were between 14 and 180 mg. For DHA, the mean amounts ranged between 131 and 273 mg/day and the median daily intakes were between 42.5 and 430 mg/day.

For all these reasons, reliable biomarkers of n-3 PUFA status are necessary to validate dietary intake data (Flock *et al.*, 2013). Significant progress has been made over the last decade and several markers of EPA and DHA are now available, including levels in plasma, erythrocytes and adipose tissue. The use of blood markers of fatty acid intake has made it possible to evaluate outcome measures related to disease. Plasma levels of fatty acids reflect intake over the past few days, whereas adipose tissue levels of fatty acids are more reflective of longer-term fatty acid intake. The Omega-3 Index (Sala-Vila *et al.*, 2011; Schacky, 2014), i.e. the erythrocyte content of EPA and DHA, is a useful biomarker of n-3 PUFA status, and the use of this standardised assessment method is important for assessing n-3 PUFA status and the biological effects of EPA and DHA intake.

5. Safety of increased EPA and DHA intake

The primary concerns with regard to the safety of omega-3 fatty acids are its effects on glycaemic control in diabetes, reduced platelet aggregation/increased bleeding time and adverse immunological effects (EFSA, 2012). Long-term human intervention studies that have investigated the effects of supplemental intakes of EPA and DHA, either alone or in combination, at amounts up to about 1 g/day on a variety of health outcomes (e.g. cardiovascular, neurological, immunological), have generally reported no adverse effects in relation to the consumption of EPA or DHA at these levels of intake.

The GISSI Prevenzione trial in 1999, the JELIS study (Yokoyama *et al.*, 2007) and the GISSI-HF Investigators (2008) study reported no clinically relevant adverse effects in over 35, 000 individuals. Over 10 years ago, the US Food and Drug Administration (FDA) determined that intakes of EPA and DHA of up to 3 g/day are safe for the general population. In 2011, the Norwegian Scientific Committee for Food Safety conducted a safety review of EPA and DHA and found no adverse effect on bleeding time, with levels as high as 6.9 g/day (Froyland *et al.*, 2011). More recently, EFSA (2012) concluded that intakes up to about 5 g/day of EPA and DHA combined do not appear to increase the risk of bleeding complications and spontaneous bleeding episodes or affect glucose homeostasis, immune function or lipid peroxidation, provided that the oxidative stability of the EPA and DHA is guaranteed. EFSA also concluded that supplemental intakes of EPA alone up to 1.8 g/day do not raise safety concerns for adults. Hence, no concerns are warranted about the safety of targeting a DIRV and an NRV of up to 500 mg/day (Harris *et al.*, 2009).

Consumption of fish raises the issue of human exposure to methyl mercury, a toxic form of mercury found in long-lived fish and predators at the top of the food chain, such as king mackerel, swordfish, shark, tilefish and albacore tuna. Although public health advice has been given for women who may become pregnant and for pregnant women, nursing mothers and young children to avoid certain types of fish potentially high in mercury, risk-benefit analyses indicate that lowering fish consumption would have serious public health consequences (Cohen *et al*., 2005; Mozaffarian and Rimm, 2006; Wennberg *et al*, 2012; Hughner *et al*., 2012; European Food Safety Authority, 2014). The messages about fish consumption should therefore not discourage individuals from eating fish; rather, they should encourage the replacement of high-mercury fish with low-mercury fish (US Food and Drug Administration and Environmental Protection Agency, 2014). In addition, fish oils used in food (dietary) supplements contain little or no mercury (Foran *et al*., 2003).

6. Summary and Conclusion

Many of the concerns about establishing DIRVs and an NRV have been addressed or resolved over the last 10 years. The wealth of scientific data from multiple observational cohort studies in numerous countries and human intervention trials strongly support a primary prevention benefit for EPA and DHA n-3 PUFAs relating to cardiovascular health benefits for healthy populations. EPA: DHA ratios ranging from about 1:2 to 2:1 are expected to be effective in providing positive heart health and cognitive outcomes. The rate of conversion of ALA to EPA is low (about 5%) and to DHA even lower (about 0.5%), and this degree of conversion is regarded as being insufficient to achieve protective tissue levels associated with cardiovascular benefits. Hence, the health benefits can only be achieved through direct intake of these fatty acids. Despite the fact that a specific ratio of EPA and DHA is not known or that all their physiological beneficial effects have not yet been elucidated, it should still be possible to define a DIRV and an NRV for the general healthy population.

Bearing in mind that the pathophysiology of CVD is the same, whether for a first heart attack or a second, the benefits relate not only to healthy individuals but also to those who may have suffered adverse cardiovascular events. With regard to safety, intakes of EPA and DHA of up to 5 g/day are considered to be safe for the general population. Hence, the establishment of a DIRV and NRV for EPA and DHA combined up to an intake of 500 mg/day should not be a cause for concern. Clearly, additional research is needed to identify and compare the specific effects of EPA and DHA on health outcomes. However, it is not uncommon to have DIRVs and NRVs for a mixture of nutrients (Harris *et al*., 2009). For example, the macronutrients protein, fat and carbohydrate all contain mixtures of individual components with unique physiological effects.

It has also been suggested that an approach for the setting of recommended intakes for dietary fibre could be used to set dietary targets for EPA and DHA (Flock *et al*., 2013). Dietary fibre is the edible, non-digestible component of carbohydrates found in plants, whereas functional fibres are isolated or extracted from natural sources. This distinction bears similarities to EPA and DHA intake, where fish is the main dietary sources, and fish oils containing EPA and DHA in so-called functional foods and food supplements provide auxiliary sources. It is worth noting that the evidence supporting the physiological benefits of EPA and DHA is greater than for those benefits attributed to dietary fibre.
In conclusion, there is a compelling rationale based on overwhelming scientific evidence that justifies the establishment of nutritionally achievable DIRVs and an NRV for EPA and DHA for the general population and individuals at every stage of their life. In view of the fact that current intakes are low compared with recommendations made to date, it is important to emphasise that enormous public health benefits and significant cost savings would be expected to accrue from new DIRVs and an NRV for these omega-3 fatty acids.

From a nutrition policy perspective, having an NRV for EPA and DHA makes it part of an overall public health policy and allows intake values to be compared with the NRV to determine whether a given population is consuming the recommended intake. Having an NRV would help develop public health messages for which there is convincing evidence of the health-enhancing effects. Health professionals, such as physicians, dieticians, nutritionists and nurses who offer nutritional advice, as well as regulatory agencies and researchers, would then all know how strong the science is behind the recommendations, and that the evidence has been through a rigorous and transparent evaluation process. An NRV would also provide the basis for commercial communications and for nutrition content claims and health claims on food and food supplement products (Biesalski *et al.* 2013; Lupton *et al.* 2014).

7. Recommendation

It is therefore proposed that the CCNFSDU consider new work on the establishment of a new NRV for omega-3 fatty acids based on EPA and DHA in order to achieve better public health and information to consumers. A Project Document is presented in Appendix II.

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Global Recommendations for EPA and DHA Intake
(As of 30 June 2014)

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
Global	World Health Organization (WHO)[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	
			Pregnant/Lactating Women	▪ EPA + DHA: 0.3 g/d of which at least should be 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 w-3 and w-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
Australia	National Heart Foundation of Australia[8]	Expert Scientific Organization	General adult population to lower risk of CHD	▪ 500 mg EPA + DHA per day, obtained through fish, fish oil capsules, or enriched foods & drinks	2008
			Patients with documented CHD	▪ 1000 mg EPA + DHA per day, obtained through fish, fish oil capsules, or enriched foods & drinks	
			Patients with	▪ 1200mg of EPA + DHA	

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
			hypertriglyceridemia	per day, obtained through fish, fish oil capsules or enriched foods & drinks as first-line therapy ▪ Increase to 4000 mg of EPA +DHA per day, as needed.	
	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 (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	

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				(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	
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
			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
	Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts)[13]	Expert Scientific Organization	General Adult Population for Cardiovascular Disease Risk Reduction	▪ Fish at least twice a week, one of which to be oily fish.	2012
	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	2008

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				▪ 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)	
	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 derive exclusively from natural food sources, and use of nutraceutical and/or pharmacological supplements may be considered	
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 ▪ EPA < DHA	
			Infants & Toddlers (6 months to 3 years)	▪ 70mg DHA /day	

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
			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	
Austria	Austrian Society for Nutrition[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[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	2012-2013

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				fish, the use of supplements with the Omega-3 fatty acid DHA is recommended	
Switzerland	Swiss Society for Nutrition Research / Swiss Nutrition Association[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	Pregnant & nursing women	▪ 250mg DHA / day	2004
			General adult population (primary cardioprevention)	▪ Two servings of fatty fish/wk	
			secondary cardioprevention	▪ 1g EPA+DHA per day	
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	

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
			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]	• n-3 fatty acids from fish: 450 mg/day	2006
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	
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 chain *n-3* fatty acids ▪ weekly intake of 1.5g of EPA + DHA	1999
	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	General Adult Population	▪ Regular intake of fish and	2005

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
		Scientific Organization		other sources of omega 3 fatty acids (at least two servings of fish per week)	
	Irish Heart Foundation[54]	Expert Scientific Organization	General Adult Population	▪ 200 mg/day long-chain fatty acids	
	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 containing fish per week week)	
Italy	Italian Ministry of Health[52]	Authoritative Body	Pregnant and Nursing Women	▪ Vegan women should consume foods rich in DHA	2007
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
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

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
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 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	2003
	March of Dimes[34]	Expert Scientific Organization	Pregnant and Nursing Women	▪ 200 mg DHA/day	2009
	National Heart, Lung, and Blood Institute, National Cholesterol	Authoritative Body	Persons with CHD or multiple risk factors for	▪ Supported AHA recommendation to	2001

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
	Education Program[35]		CHD	include fish as part of a CHD risk reduction diet. Higher dietary intakes of n-3 PUFAs are an option for reducing CHD risk	
	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	All adults without CHD[37]	▪ Eat fish (particularly fatty fish) at least two times a week; include oils and foods rich in ALA	2002
			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 CHD[37]	▪ Consume approximately 1 g/day of EPA+DHA preferably from oily fish. EPA+DHA supplements could be considered in consultation with the physician	2002
			Patients with high triglycerides[37]	▪ 2-4 g/day EPA+DHA as capsules under a physician's care	2002
			Patients with high triglycerides[51]	• …increasing consumption of marine-based omega-3 products,…, will further optimize triglyceride-lowering efforts.	2011
			Cardiovascular Disease	▪ Consume fish, especially	2011

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
			Risk Reduction in Women[38]	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	
			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	▪ Increase the amount and variety of seafood consumed by choosing seafood in place of some meat and poultry	2010
			Pregnant or breastfeeding women	▪ consume at least 8 and up to 12 ounces of a variety of seafood per	

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				week	
	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 Organization	Nursing Women	• The mother's diet should 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	2012

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				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 Welfare, Canada[42]	Authoritative Body	General adult population	• 1.2-1.6 g/day total n-3 PUFAs (ALA, EPA, DHA)	1990
	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	

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				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 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	

Country/Region	Organization	Org. Type	Target Population	Recommendation	Publication Date
				day	
			Pregnant Women	• 1.8g total omega-3 per day	
			Nursing Women	• 1.8g total omega-3 per day	
			Acute ST Segment Elevation Myocardial Infarction[46]	• Increased intake of omega 3 – fatty acids (1g daily) is beneficial. • Eat fish at least twice a week.	
Malaysia	Ministry of Health	Authoritative Body	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	2008
			For people with high risk or secondary prevention	• 1000 mg EPA + DHA/day as supplement for people who don't eat fish	2011
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 II

Project Document

1. Purpose and Scope of the Standard

The scope of the proposed new work is to develop and add a new Codex nutrient reference value (NRV) for omega 3 fatty acids based on docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) intended for general population for labelling purpose in the *Codex Guidelines on Nutrition Labelling (CAC/GL 2-1985).*

2. Relevance and Timeliness

WHO, FAO and various other international / national bodies in recent years have published extensive researches and recommended intakes of DHA and EPA based omega-3 fatty acids for the population. These available data will contribute to developing an internationally harmonized NRV for such nutrient by the Codex Committee on Nutrition and Foods for Special Dietary Uses (CCNFSDU) under its current work on the addition or revision of NRVs for labelling purposes in the *Codex Guidelines on Nutrition Labelling (CAC/GL 2-1985).*

3. Main Aspects to be Covered

The main aspects to be covered under the proposed new work is to establish a new Codex NRV for omega-3 fatty acids based on DHA and EPA for the general population, and add to the *Codex Guidelines on Nutrition Labelling (CAC/GL 2-1985).*

4. Assessment Against the *Criteria for the Establishment of Work Priorities*

The proposed work fulfills the criteria on consumer protection from the point of health, food safety, ensuring fair practices in the food trade and taking into account the identified needs of developing countries.

Strong scientific data has supported a primary prevention benefit for omega 3 fatty acids based on DHA and EPA relating to cardiovascular health for the general population. In addition, overwhelming scientific evidence justifies the establishment of nutritionally achievable daily intake reference values (DIRVs) and an NRV for EPA and DHA for general population and individuals at every stage of their life. In view of the fact that current intakes are low compared with the recommendations made to date, it is important to note that enormous public health benefits and significant medical cost savings would be expected to accrue from new DIRVs and an NRV on these omega-3 fatty acids.

Furthermore, from a nutrition policy perspective, having an NRV for EPA and DHA makes it part of an overall public health policy and allows intake values to be compared with the NRV to determine whether a given population is consuming the recommended intake. Having an NRV would help develop public health messages for which there is convincing evidence of the health-enhancing effects.

The proposed new work will also help develop an internationally harmonised nutrition labelling guideline for omega-3 fatty acid content in foods that will facilitate trade.

5. Relevance to the Codex Strategic Objectives

The proposed work will contribute to the following Codex strategic objectives in the Codex Strategic Plan 2014-2019:

Strategic Goal 1: Establish international food standards that address current and emerging food issues.

The proposed new work will help address the emerging scientific evidence on the population health benefits brought by recommended dietary intake of omega-3 fatty acids.
Strategic Goal 2: Ensure consistent use of risk analysis principles and scientific advice.

The development of the new NRV will be consistent with the use of scientific advice and risk assessment principles. Scientific advice from FAO/WHO as well as other international / national scientific bodies (identified and summarised in Appendix 1 of this paper) will be considered.

6. Information on the Relation Between the Proposal and other Existing Codex Documents

The proposed new work is relevant to the *Codex Guidelines on Nutrition Labelling (CAC/GL 2-1985).*

7. Identification of any Requirement for and Availability of Expert Scientific Advice

Available expert scientific advice has been identified in Appendix 1 of this paper.

8. Identification of any Need for Technical Input to the Standard from External Bodies so that this can be Planned for

No technical input from external bodies is foreseen at this moment.

9. Proposed Timeline for completion of the new work, including the start date, the proposed date for adoption at Step 5, and the proposed date for adoption by the Commission; the time frame for developing a standard should not normally exceed five years

An electronic working group (eWG) could be established during the 36th Session of the CCNFSDU including in its mandate to prepare the proposed draft NRV on omega-3 fatty acids based on DHA and EPA, for discussion and adoption by the 37th CCNFSDU Session of the CCNFSDU in 2015 with the possibility to have it adopted at Step 5/8 by the 39th Session of the Codex Alimentarius Commission (CAC) in 2016.