



## **Council for Responsible Nutrition**

1875 Eye Street, N.W., Suite 400  
Washington, D.C. 20006-5409  
(202) 872-1488 • Fax (202) 872-9594  
[www.crnusa.org](http://www.crnusa.org)

June 16, 2002

Dr. Pekka Puska  
Director, Noncommunicable Disease Prevention  
And Health Promotion  
World Health Organization  
Geneva, Switzerland

Dear Dr. Puska:

Thank you for the opportunity to consult on the World Health Organization draft documents on Diet, Health and Prevention of Chronic Diseases. The Council for Responsible Nutrition (CRN) is a nongovernmental organization (NGO) accredited by the Codex Alimentarius Commission. CRN is a trade organization that represents companies that manufacture ingredients and products such as dietary/food supplements and functional foods that contain added vitamins, minerals, and other ingredients. CRN is a science-based organization that is committed to improvement of human health and wellbeing through improved diet and nutrition

We appreciate the opportunity to make an oral comment at the WHO headquarters in Geneva or April 16 and your very appropriate decision to extend the written consultation period by 60 days. Three comments are submitted by CRN:

1. Comment prepared by Dr. John Hathcock, a CRN staff member.
2. Comment by Dr. Louis Mejia, a staff member for ADM Corporation, CRN member company.
3. Comment by Dr. Klaus Kraemer, a staff member for BASF Corporation, a CRN member company.

Sincerely,

John N. Hathcock, Ph.D.  
Vice President, Nutritional and Regulatory Science

### Attachments

1. Comment by CRN (continuation of this file)
2. Comment by ADM (continuation of this file)
3. Comment by BASF (separate file)

**Comment on World Health Organization Documents on  
DIET, NUTRITION AND THE PREVENTION OF CHRONIC DISEASES**

---

**INTRODUCTION**

The Council for Responsible Nutrition (CRN) has two general types of concerns about this consultation on a most important topic. Firstly, the policy options—the practical feasibility of recommendations were given no apparent consideration or recognition that cultural, economic, and technical factors can create barriers that may make the recommended actions and hypothetical benefits completely unavailable. Secondly, several of the scientific discussions are simply inadequate—there are serious omissions, errors and misdirected emphasis. In the instances of misdirected emphasis, the discussion and conclusions may be correct but the emphasis in the paper is such that it would encourage inappropriate policy choices.

**GENERAL COMMENTS**

The scientific data now available are sufficient to show clearly the importance of overall dietary pattern, macronutrient intake and balance, intakes of vitamins and intakes of minerals on the incidence of the chronic degenerative diseases that are the focus of these documents. In addition, diet has important effects on acute but recurring infectious diseases, thus amounting to chronic relationships.

The draft documents emphasize the importance of dietary patterns and macronutrient intake on the chronic degenerative diseases, but do not give adequate consideration to the feasibility of changing dietary patterns and nutrient intakes. The practical feasibility of recommendations on diet and chronic disease is an essential consideration for positive effects on the public health.

In some cases, the emphasis in the draft documents misdirects attention away from the nutrients that can have real beneficial impacts, and toward the dietary patterns and nutrient intakes that make no difference in the disease risk. For example, in relation to osteoporosis, the discussion of the lack of effects of the macronutrients is, quite unjustifiably, the main topic of the review. The strong impacts of calcium and vitamin D on osteoporosis are acknowledged very late and are not fully discussed. Such misdirected emphasis carries the potential for distracting attention and support away from options that could provide improvement to the public health. Such mistakes should be eliminated in a thorough scientific and policy review before these documents are worthy of forming the basis of public policy. Also, these corrections are necessary before the documents and recommendations can attract the wide base of national support that is required for effective implementation.

## **SOME EXAMPLES OF CORECTIONS NEEDED**

### Section 3.4

The health advantages of improved micronutrient intakes should be listed in Section 3.4. Examples that should be included include iron, zinc and vitamin A intakes in developing countries, and folic acid, calcium, and perhaps the antioxidant nutrients in countries with higher incomes and broader food choices.

The last paragraph in Section 3 completely omits discussion of the nutrient intakes that are quite feasible to improve, e.g., calcium, folic acid, iron, zinc, and vitamin A. This omission is a severe detriment to the value of the document. These nutrients and intake goals should be listed in Table 2.

### Table 3

There is not sufficient scientific support for the statement that dietary NSP (fiber) itself protects against weight gain and obesity. It is true that consumption of diets high in dietary fiber are associated with such protection, but those diets are lower in energy, digestible carbohydrate, and perhaps protein. The scientific evidence is very clear that it is the decreased intakes of these components, rather than increased intake of dietary fiber itself that are responsible for the health improvements. Causality must be correctly attributed to assure that dietary recommends are appropriate and effective, and causality is incorrectly attributed in these discussions.

### Table 6

The characterization that the evidence is convincing that vitamin E supplements have no relationship to cardiovascular diseases is simply wrong. The evidence is mixed, with some evidence being supportive, some being strongly contrary, and some being unclear. Vitamin E should be moved to the “possible” category for decreased risk.

Blood cholesterol, but not dietary cholesterol, has a convincing relationship to risk of heart disease. Dietary cholesterol has little relationship to blood cholesterol levels. This topic should be reviewed again, and dietary cholesterol should be moved to the insufficient category for increased risk.

### Section 4.4

The assertion of global increases in cancer mortality are not properly described in the context of increasing life span, proper adjustment for age, and failure of the populations to die at younger ages of causes other than noncommunicable diseases. This failure leads to the erroneous conclusion that the dietary changes with increased industrialization and higher income increase the risk of cancer.

### Table 7

The table make a serious error by ignoring the strong evidence that increased selenium intake would decrease the risk of cancer in many populations. The scientific evidence of an anti-cancer effect of dietary selenium is very strong—mechanistic studies, animal assays and a long-duration human intervention trial. The long-term clinical intervention trial by Clark and colleagues (Clark, et al., *JAMA*, December 1996) is quite compelling, but nonetheless public health and research administrators have judged the evidence “insufficient” and are now initiating an additional multinational clinical trial. This decision effectively ignores the fact that the clinical trial by Clark and coworkers was stopped early because it would have been unethical to continue it, thereby denying the benefits to the subjects randomized into the placebo group. The evidence for a preventive effect of selenium is much stronger than for an increased risk with most of the substances listed as having convincing evidence.

This section needs a completely new review and a major redirection of the conclusions. Public health policy based on the current document would be a disservice to the world's consumers.

#### Section 4.6

The subsection on diet and disease begins with a very mistaken and misdirected emphasis. The emphasis should be on the successful reductions in risk with adequate calcium and vitamin D, rather than the true but useless description that most of the diet has no impact on risk of osteoporosis. The correction needed is much greater than just rewriting this paragraph. The entire detailed review on diet and osteoporosis should be redrafted to create an emphasis on those dietary components with strong effects on osteoporosis, rather than the current emphasis on most dietary components with no effect on this debilitating disease.

#### Table 12

The emphasis on the clinically obvious osteoporosis leads to an erroneous conclusion—that no dietary components have any impact on this disease until the age of 50-60 years. In fact, calcium and vitamin D (and perhaps vitamin K) have major impacts on bone mineral density (BMD) at a much earlier age (perhaps between puberty and 30 years). Dietary changes to increase BMD between puberty and 30 years will lead to reduce risk of osteoporosis at 50-60 years and older ages. This table and related recommendations, and the main review of osteoporosis should be redrafted to reflect these realities. The misdirected emphasis is a serious obstacle to improving consumers' health.

#### CRN's Conclusions

The examples selected amply demonstrate that there should be detailed and serious reassessment of the scientific evidence. Likewise, the policy conclusions should be judged for beneficial public health impact and practical feasibility. These additional steps are necessary if the WHO wants the conclusions and policy recommendations that flow out of these documents to have credibility and gain the wide national support needed for implementation and benefits the consumers' health. CRN urges the WHO to delay any policy considerations and decisions until new reviews and redrafting of these documents can be completed and subjected to a broad-based, public peer review and policy analysis. Such a full vetting of the scientific documents and policy conclusions is essential to reach an international consensus and implementation.

Joint WHO/FAO Expert Consultation  
Comments to Draft Document:  
Diet Nutrition and the Prevention of Chronic Diseases

1) Criteria used for: “Strength of Evidence”

A) There appears to be some degree of inconsistency in applying equal clinical vs. epidemiological criteria among different factors linked (positively or negatively) to different disease conditions. To illustrate this point, one can examine the proposed ranking of trans-fatty acids vs. plant sterols/stanols vs. Vitamin E supplements in the context of Cardio Vascular Disease (CVD). Trans-fatty acids are ranked as having “convincing” evidence for increasing the risk of CVD yet, plant sterol/stanols are ranked as “probable” for decreasing risk. In reality, the trans-fatty acid randomized Control Trials (RCT) data tends to be inconsistent but the plant sterol/stanol data tends to be rather consistent. The only additional data that trans-fatty acids have over plant sterols/stanols is consistent epidemiological data (the weakest data) which elevates trans-fatty acids to the “convincing category” for increasing CVD. Neither trans-fatty acids nor plant sterol/stanols have been examined directly in a RCT for the end point of CVD (mortality/recurring MI) either in a primary or secondary prevention scenario. Vitamin E on the other hand, like trans-fatty acids, has consistent epidemiological data supporting a potential beneficial effect in decreasing CVD risk. However, the consultation panel feels that the current RCT trials outweigh the epidemiological support and Vitamin E is ranked lower than trans-fatty acids (or vice versa). In addition, no weight is given to the lack of outcome in hard end points regarding CVD for trans-fatty acids but is given weight for plant sterols/stanols; as a result plant sterol/stanols are also ranked lower than trans-fatty acids. In summary, we suggest a more careful consideration on the ranking criteria used, particularly on the consistency of their application. Based on this re-analysis, adjustments in the ranking levels may become necessary.

B) Difference between “Probable” and “Possible”

The difference between these two terms for ranking the strength of scientific evidence may be too subtle. This may become a more critical issue when translating into other languages. We recommend re-examining this terminology. A suggestion would be: “convincing”, “most probable”, “possible”, etc.

2. Beta-Carotene and Cardiovascular Disease

To our knowledge,  $\beta$ -carotene supplements are not related to an increase in CVD. Previous observations have suggested an association between  $\beta$ -carotene and cancer in active smokers (not discussed in cancer section of the document). However, there is not significant scientific data supporting a negative relationship between  $\beta$ -carotene and CVD.

3. Vitamin E and Periodontal Disease

Vitamin E is mentioned in the context of several disease conditions as having no effect or low/insufficient evidence to be related to certain disease conditions; one of these is periodontal disease. We are sure there are also many other nutrients and bioactive components that are also known not to have an effect under the disease condition under consideration. However, these substances are not mentioned. This repetitive situation for Vitamin E may have an unfair “negative image” effect on this vitamin. We suggest deleting “Vitamin E supplementation” from the no-relationship column on table 11 (page 40).

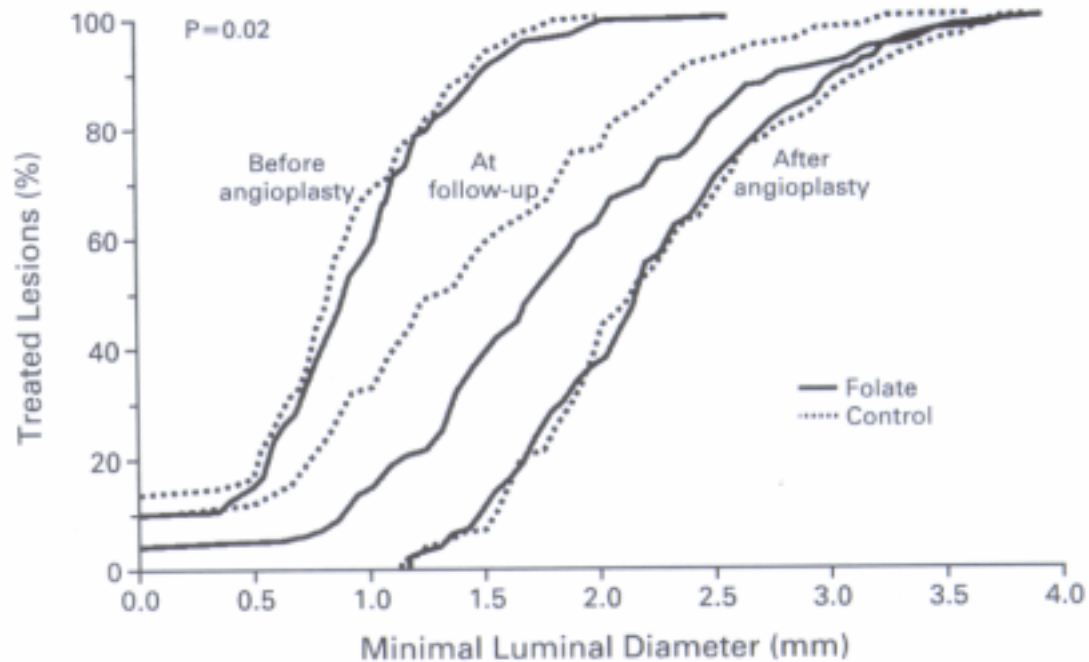
**Data on folates and B-vitamins in the prevention of cardiovascular disease (CVD) are more convincing than presented in the WHO report**

# Folates and B-Vitamins in the Prevention of Cardiovascular Disease (CVD)

- **Elevated plasma homocysteine is independent risk factor for coronary heart, cerebrovascular and vascular disease.**  
[Ann Intern Med 1999; 131:363-375 ]
- **Folic acid (0.4-5.0 mg/d) lowers homocysteine by 25%. Further lowering can be achieved by vitamin B<sub>12</sub>, and vitamin B<sub>6</sub>.**  
[BMJ 1998; 316:894-898; AJCN 2001; 73:759-764]
- **Plasma vitamin B<sub>2</sub> is an independent determinant of homocysteine in subjects homocygous for MTHFR C677T polymorphism.**  
[J Nutr 2002; 132:283-288]

**Optimal intake of B-vitamins can reduce CVD risk substantially.**

# Distribution of Luminal Diameters with and without Homocysteine Lowering after Coronary Angioplasty



Patients received folic acid (1mg), B12 (400µg) and B6 (10mg) for 6 months.

[N Eng J Med 2001; **345**:1593-1600]

**Vitamin E has never been shown to be hazardous in patients with CVD as stated in the WHO report**

# Observational Studies

## Nurses' Health Study (NHS):

since 1980, n=121,700 females, age 34-59, food frequency questionnaires

8 years of follow-up: RR=0.74 (5.4-14.4 mg/day) 4<sup>th</sup> quintile

RR=0.66 (14.5-670 mg/day) 5<sup>th</sup> quintile

(Stampfer MJ et al, 1993)

## Health Professionals' Follow-up Study (HPFS):

since 1986, n=51,529 males, age 40-75, food frequency questionnaires

4 years of follow-up: RR=0.74 (median 17 mg/day) 4<sup>th</sup> quintile

RR=0.59 (median 280 mg/day) 5<sup>th</sup> quintile

(Rimm EB et al, 1993)

## Dietary Antioxidant Vitamins and Death from CHD:

since 1986, n=34,486 women, postmenopausal, food frequency questionnaire

7 years of follow-up: RR=0.38 5<sup>th</sup> quintile

(Kushi LH et al, 1996)

# Summary of Prospective Vitamin E Clinical Trials

Study	Dose	Primary Endpoint	Other Endpoints	Adverse Effect
ATBC (Primary and Secondary Prevention)	50 IU/day All rac AT	X (Cancer)	+	—
CHAOS (Secondary Prevention)	400 & 800 IU/day RRR-AT	+	X	X
GISSI (Secondary Prevention)	330 IU/day All rac AT	X	+	X
HOPE (Primary and Secondary Prevention)	400 IU/day natural source vitamin E	X	X	X
SPACE (Secondary Prevention)	800 IU/day RRR-AT	+	X	X
PPP (Primary Prevention)	330 IU/day All rac AT	X	+	X
ASAP (Primary Prevention)	272 IU/day RRR-AT	X	X	X

+ **positive finding**; X **no effect** ;—**negative finding**

# Vitamin E and Cardiovascular Disease

- Is there a benefit? -

Large-scale, double-blind, randomized and placebo-controlled trials\*:

Study	Year	Primary Endpoint	Vitamin E Treatment	Result
CHAOS	1996	Heart Disease	400-800 IU/d	Benefit
GISSI	1999	Heart Disease	300 IU/d	No effect
HOPE	2000	Heart Disease	400 IU/d	No effect
HPS	2002 (unpubl.)	Heart Disease	600 mg/d	No effect
ATBC	1994	Lung Cancer	50 IU/d	No effect

\* Secondary Prevention of CHD

### SPACE Study:

n=196 patients with end-stage renal disease and pre-existing CVD

800 IU/day vitamin E; follow-up 519 days (median)

→ 54% lower rate of cardiovascular outcomes, 70% lower rate of total MI

(BOAZ M et al, Lancet 2000)

### ASAP Study:

n=520 participants at risk of CVD

272 IU/d vitamin E and/or vitamin C (500 mg/d) for 3 years

→ Combination of vitamin E plus C lowered disease progression (carotid IMT) in 74% of men but not in women. No effect of vitamin E alone.

(Salonen JT et al, J Intern Med 2000)

### Primary Prevention Project:

n=4495 participants at high risk of CVD

667 IU/day vitamin E and/or aspirin (100 mg/day); follow-up 3.6 years

→ no effect of vitamin E intervention on cardiovascular endpoints. Study was stopped prematurely for ethical reasons due to aspirin benefits.

(PPP, Lancet 2001)

### SECURE Study:

n=732 patients with vascular disease or diabetes, and other risk factors

400 IU/day vitamin E and/or ACE inhibitor (ramipril, 2.5 or 10 mg/day);

follow-up 4.5 years

→ no effect of vitamin E on disease progression (carotid IMT)

(Lonn EM et al, Circulation 2001)

In epidemiological studies high vitamin E intake is associated with a lower risk of CHD.

Long-term intake of vitamin E supplements seems to benefit in the prevention of CVD (NHS and HPFS).

---

There are *no* large-scale clinical trials on the efficacy of vitamin E in primary prevention of CVD.

Large-scale trials with patients with established CVD show ambiguous results on the effect of vitamin E supplementation on cardiovascular endpoints.

## CVD - Small Clinical Trials

Numerous small clinical trials show benefits of (short-term) vitamin E supplementation on parameters of oxidative stress and vascular function:

Lower LDL susceptibility to oxidation

Improved vasodilation

Improved immune cell function

Inhibition of smooth muscle cell proliferation

Inhibition of platelet aggregation

## Diabetes, type 1:

1,800 IU/day vitamin E, for 4 months  
retinal blood flow

(Bursell SE et al, 1999)

→ improved

→ improved renal function

1,000 IU/day vitamin E, for 3 months

(Skyrme-Jones RA et al, 2000)

→ improved endothelial vasodilator function

## Diabetes, type 2:

1,200 IU/day vitamin E, for 3 months

(Devaraj S and Jialal I, 2000)

→ decreased LDL susceptibility to oxidation

→ decreased monocyte activity ( $O_2^-$  release, adhesion, cytokine release)

→ decreased C-RP levels

600 IU/day vitamin E, for 8 weeks

(Paolisso G et al, 2000)

→ improved brachial artery reactivity

## Diabetes, type 1:

1,800 IU/day vitamin E, for 4 months  
retinal blood flow

(Bursell SE et al, 1999)

→ improved

→ improved renal function

1,000 IU/day vitamin E, for 3 months

(Skyrme-Jones RA et al, 2000)

→ improved endothelial vasodilator function

## Diabetes, type 2:

1,200 IU/day vitamin E, for 3 months

(Devaraj S and Jialal I, 2000)

→ decreased LDL susceptibility to oxidation

→ decreased monocyte activity ( $O_2^-$  release, adhesion, cytokine release)

→ decreased C-RP levels

600 IU/day vitamin E, for 8 weeks

(Paolisso G et al, 2000)

→ improved brachial artery reactivity

## Food and Nutrition Board, 2000:

UL (adults): 1000 mg/day  $\alpha$ -tocopherol  
(1500 mg/day natural; 1100 mg/day synthetic)

**Insufficient data in humans!**

**Biomarker: Incidence of bleeding (rats)**

**Non-significant increase in incidence of hemorrhagic stroke in the ATBC study (smokers). No effect seen in non- smokers.**

(ATBC, N Engl J Med 1994; Ascherio A et al, Ann Intern Med 1999)

**Possibly increased progression of disease in patients with retinitis pigmentosa.** (Berson EL et al, Arch Ophthalmol 1993).

# CVD - Ongoing Clinical Trials I

Study	Institution	Participants	Treatment	Duration
<b>CLIPS</b>	Multi-center	350	Antioxidants (600 mg Vitamin E, 250 mg Vitamin C, 20 mg beta-carotene) plus aspirin	Up to 4 years (to 2002)
<b>WAVE</b>	Multi-center	420 women ≥ 38 years	800 IU Vitamin E, 1000 mg Vitamin C and/or HRT	3 years (to 2002)
<b>Carotid Athero- sclerosis Trial</b>	University of Texas	120	1200 IU vitamin E	2 years

## CVD - Ongoing Clinical Trials II

Study	Participants	Treatment	Duration
<b>SU.VI.MAX</b>	13,000 women ≥ 35 years, men ≥ 45 years	30 mg Vitamin E, 120 mg Vitamin C, 6 mg beta-carotene, 100 µg Se, 20 mg Zn	8 years (to 2003)
<b>WACS</b>	8,000 women ≥ 40 years	600 IU vitamin E, 50 mg beta-carotene on alternate; 500 mg vitamin E daily	5 years (to 2002) extended (to 2006)
<b>WHS</b>	39,876 women, ≥ 45 years	600 IU vitamin E and/or aspirin on alternate days	5 years (to 2004)
<b>PHS II</b>	15,000 male physicians ≥ 55 years	400 IU Vitamin E, 50 mg beta-carotene on alternate; 500 mg vitamin C, multivitamin daily	5 years (to 2002) extended (to 2007)

## Conclusions and Future Directions

Observational studies show a benefit from a high dietary intake of vitamin E and particularly from long-term intake of vitamin E supplements on the risk of CVD.

Good evidence from animal studies exists that vitamin E prevents (early) atherosclerosis and lowers progression of disease.

New assays and new biomarkers are needed for determining the biological activity of vitamin E. Effective disease-related biomarkers are still missing.

The effectiveness of vitamin E on primary prevention of CVD needs to be established.

The possible benefit of vitamin E supplementation in patients at high-risk of CVD needs to be further confirmed in larger trials.