CAPSUGEL®

Impact of Antioxidants on Health Preservation and Healthcare Costs.

An Opportunity for the Industry?

1ST FIT&FAST® INTERNATIONAL SYMPOSIUM

Impact of Antioxidants on Health Preservation and Healthcare Costs. An opportunity for the industry?

Capsugel, a division of Warner Lambert, is the company's globalised capsule business. Headquartered in USA, Capsugel is the world's largest producer of hard gelatin capsules.

Launched in 1995, the Fit&Fast programme has been set up specifically to help manufacturers of dietary supplements to bring products in hard gelatin capsule form to the market as quickly as possible.

It represents a network resource of international marketing and technical consultants offering expertise in: formulation, regulatory requirements and international standards, filling line solutions, marketing consultancy and packaging design service.

Capsugel was pleased to present in Paris, April 18, 1996, the first Fit&Fast® Symposium on "The Impact of antioxidants on health preservation and healthcare costs. An opportunity for the industry?", chaired by Maurice Hanssen, Director of the European Health Products Manufacturers' Association (EHPM).

The purpose, in organising this Conference and Panel discussion, was to help clarifying the role of antioxidants in degenerative diseases and make recommandations on the regulatory aspect in order to improve their status, according to the evidence of their impact.

In that respect, we are convinced that Pr A.T. Diplock's expertise, as well as Mr Hasslberger's and Dr A. Dickinson's presentations helped the participants to have a better view on the subject.

Capsugel was proud to organise this Symposium as part of its commitment to the development of the Health Supplements market in Europe.

Your feedback will tell us if we achieved this objective. We are looking forward to hearing from you.

CAPSUGEL®

Health care cost savings from better nutrition: economic impact of antioxidant intake

By Annette Dickinson, Ph.D.
Director of Scientific and Regulatory Affairs, Council for Responsible Nutrition
Paris, April 1996

Health care cost savings from better nutrition: economic impact of antioxidant intake

By Annette Dickinson, Ph.D. Director of Scientific and Regulatory Affairs, Council for Responsible Nutrition, Washington, U.S.A.

Paris, April 1996

Pracon study abstract

Objectives: The potential decrease in the number and cost of hospitalizations related to an increased intake of antioxidant vitamins is estimated for the Medicare program and nationally.

Methods: United States hospitalization data were obtained from the National Hospital Discharge Survey and California Acute-Care Hospitalization data. Medicare data were obtained from the MEDPAR file. The proportional change in the number of hospitalizations related to increased antioxidant vitamin intake was calculated using relative risks reported in the literature.

Results: The estimated conservative reduction in the number of hospitalizations for Medicare enrollees, given increased intake of antioxidants, is 302,748, with related potential cost savings of $ 1.7 billion for the Medicare program. Similarly, 595,570 hospitalizations in the United States might be avoided if diets sufficiently rich in antioxidants are consumed, leading to potential cost savings of $ 8.8 billion for the United States health care system.

Conclusions: The current intense focus on health care reform emphasizes the importance of preventive medicine. The potential economic impact of increased antioxidant vitamin intake is substantial and should figure prominently in the nation's stategy for implementing health care reform.

Lecture

Health care costs are escalating in U.S. — as in other western countries — and there is great interest in the potential for reducing health care costs through health promotion and disease prevention. In a classic article published in 1981, Doll and Peto estimated that about 35% of cancers were related to dietary habits and therefore at least potentially preventable through dietary improvements.

In the United States, there has been great hope that consumers who are given full information about the risks and benefits of particular foods will act on that information to improve their food choices and ultimately improve their health. Nutrition labeling was adopted in the U.S. in 1973, as a voluntary initiative to help people make better food choices, but the original nutrition label was not very impressive in a graphic sense, and failed to provide full information on some of the very food components which appeared to have the greatest impact on health, namely saturated fat, cholesterol, and dietary fiber.

A new approach seemed to be needed. In the course of developing and defending the new approach, FDA retained the Research Triangle Institute to prepare an economic analysis showing that better nutrition information could lead to better health and fewer deaths. These savings could be quantified in terms of the dollar value of the life-years gained through disease prevention. It was FDA's economic analysis of the new approach to nutrition labeling that initially gave us the idea for the Pracon study, which I am going to discuss today. Let me spend just a few minutes providing some background information on the new U.S. approach to food labeling and FDA's economic analysis of its benefits, before discussing the Pracon study.

In 1990, Congress passed the Nutrition Labeling and Education Act (NLEA), which mandated a new format for nutrition labeling, permitted a wide variety of "nutrient content claims", and for the first time authorized FDA to permit "health claims" to appear in food labels, specifically highlighting the relationship between specific nutrients and various chronic diseases.

In implementing the NLEA, FDA defined several "nutrient content claims" such as "low fat", "reduced fat", "no cholesterol" and "high in fiber", with the idea that these terms would draw consumers to healthier foods. In addition, it was believed that these terms would have a marketing advantage and would therefore encourage manufacturers to produce more foods eligible to bear claims such as these.

Health claims were the greatest innovation permitted by NLEA. Before 1990, FDA had historically considered any mention of a disease condition to constitute a "drug claim", and such claims were prohibited for food products. As it became clear during the 1980's that diets low in fat, low in cholesterol, and high in fiber

were very likely to have a substantial impact in preventing heart disease and cancer, food manufacturers became more aggressive in their efforts to convey that information to consumers. In 1984, the Kellogg company joined forces with the National Cancer Institute to launch a nationwide campaign to tell consumers that diets high in fiber may help prevent cancer. FDA seriously considered taking legal action against Kellogg by seizing All-Bran breakfast cereal as a "misbranded new drug," but cooler heads prevailed and ultimately FDA began instead to develop guidelines for health claims. Four groups, including the Kellogg Company and the Council for Responsible Nutrition, filed separate petitions with FDA requesting that the agency develop guidelines or regulations permitting health claims. However, before FDA could issue final regulations, Congress passed NLEA which clearly gave FDA the legal authority to permit such claims and which set forth a priority list of 10 claims to be evaluated first.

A petition process was established to permit manufacturers or others to request approval of additional claims, after the first ten had been evaluated.

FDA ultimately approved 8 health claims. Three of these related to the benefits of eating "less" of something: less fat and less salt. Specifically, FDA approved health claims regarding the effect of low fat diets in reducing cancer and heart disease, and the effects of low salt diets in reducing the risk of hypertension.

Only two of the approved claims related to the benefits of consuming "more" of a specific nutrient. FDA permitted claims regarding the benefit of calcium in reducing the risk of osteoporosis, and the benefits of folic acid in reducing the risk of neural tube birth defects.

In three cases, FDA declined to approve a health claim for specific nutrients, but did approve a health claim for foods naturally containing those nutrients. FDA concluded that a claim was not justified for fiber *per se*, but did approve claims that high-fiber diets could reduce the risk of both cancer and heart disease. Such claims are permitted on foods which are naturally "good sources" of dietary fiber or soluble fiber. This applies principally to fruits, vegetables, and grain products. FDA also concluded that a specific nutrient claim was not justified for any of the antioxidant vitamins, but did approve a health claim for fruits and vegetables which are naturally "good sources" of vitamin C and/or beta-carotene. (A "good source" of a nutrient is a food that provides at least 10% of the Daily Value, per serving.)

In the past month, FDA has proposed to approve a new fiber claim, specific to oat bran or oatmeal. The claim relates to decreasing the risk of heart disease, and would be allowed for foods which contain at least 20 grams per serving of oatmeal or at least 13 grams per serving of oat bran, if these ingredients naturally provide at least 1 gram of the soluble fiber beta-glucan per serving. This proposed approval is an encouraging

sign that FDA is in fact receptive to new health claims. The dairy industry has recently submitted a petition for a health claim relating to the effect of high-calcium diets in reducing the risk of hypertension, and the Council for Responsible Nutrition is currently preparing a petition for a health claim regarding the effect of folic acid in reducing the risk of heart disease through reducing blood levels of homocysteine.

The health claims provisions of NLEA may ultimately have the greatest impact on the health of consumers in the U.S., but the provision which had the most massive impact on all food labels was the new nutrition labeling format. In implementing NLEA, FDA took the opportunity to design a strikingly bold nutrition label. It not only provides more relevant information to consumers, but it practically leaps out and grabs the shopper's attention. (Show examples of the old and new nutrition labeling, for the same brand of the same product, in the same size container).

FDA's new nutrition labeling format required more than 8,900 food manufacturers to change more than 257,000 different labels — a massive and expensive undertaking. As mentioned earlier, FDA contracted with the Research Triangle Institute to prepare an estimate of the costs of these label changes, compared to the health benefits expected to accrue over a period of 20 years.

The cost of the label changes was estimated to be $1.7 billion, and the benefits were estimated to be $3.6 billion over a 20-year period. This amounts to an average of only $180 million per year in benefits, for that 20-year period.

The total $3.6 billion benefit is based on the assumption that 39,000 cases of cancer and heart disease would be avoided over the 20-year period, and that 13,000 deaths would be avoided. This would result in a savings of 81,000 life-years, with a dollar value of $3.6 billion.

To CRN and to many observers, these figures seemed surprisingly low, but there were several reasons for the low estimates of impact. First, these figures were based solely on the presumed impact of nutrition labeling, and did not take into account any effect of health claims or of educational campaigns that might be undertaken by industry or by private organizations or by the government itself. Second, it was assumed that only a minority of consumers would actually read and understand nutrition labeling. Third, it was assumed that only a fraction of those who do read and understand nutrition labeling will actually make dietary changes based on that information. At the same time that the NLEA was being implemented, the dietary supplement industry was facing numerous challenges. FDA had issued a discussion document suggesting the possibility of dosage limits on many products. The agency had also expressed the view that some types of products should be regulated as drugs rather than dietary supplements. Also FDA seemed to be reluctant to approve health claims for dietary supplements. In

response to these challenges, the dietary supplement industry began to work for the passage of legislation which would assure continued access to the full range of dietary supplement products.

Also, CRN and other groups submitted extensive comments to FDA, seeking to support health claims for several nutrients, including omega-3 fatty acids and the antioxidant vitamins.

In order to provide additional support for a health claim for antioxidant vitamins, and in order to demonstrate that optimal supplementation with these vitamins could help reduce health care costs, CRN initiated the Pracon study in 1993. Pracon is an economic analysis firm in the Washington area, a subsidiary of the Excerpta Medica group of companies. They specialize in economic analyses of health care alternatives. For example, they frequently develop the economic data required to be submitted with New Drug Applications, illustrating the economic impact of a new pharmaceutical product, compared to existing treatments. The two expert analysts who worked on the CRN project are no longer with Pracon: Dr. Steven Pashko, the senior analyst, is now with Bristol-Myers Squibb and Monica Sena is now with Marion Merrell-Dow.

The goal of the Pracon project was to quantify the health care cost savings that could be realized if consumers obtained optimal amounts of the antioxidant vitamins, especially vitamin C and vitamin E and beta-carotene. The focus was on hospitalization costs, because databases were available which would permit detailed analysis of such costs, for specific disease conditions. Since public payment of health care costs is a major issue, the study also provided an estimate of the total Medicare costs which might be saved through disease prevention, for specific diseases affected by antioxidant vitamin status. Three major databases were utilized:

(1) The National Hospital Discharge Survey, which provides national data on the number of people hospitalized and the duration of stay, for specific disease conditions (but no information on costs).

(2) The California Hospital Discharge Database, which provides cost data for hospitalizations for specific disease conditions.

(3) The Medicare Provider Analysis and Review, which is a complete database of all medicare expenses, annually, for specific disease conditions.

We originally decided to focus on four disease conditions: coronary heart disease, stomach cancer, lung cancer, and cataracts. These conditions were selected after a literature review demonstrated the availability of strong studies showing a benefit of antioxidant vitamins in decreasing the risk of these chronic diseases.

In 1994, we dropped lung cancer from the report, because of the negative findings of the Finnish study

regarding beta-carotene and lung cancer. Recent negative findings on high-dose beta-carotene were also reported in two other studies. It is obvious that any economic analysis can only be as strong as the underlying scientific evidence regarding the effect of any agent on a disease condition. While the evidence is strong that diets high in beta-carotene are protective against lung cancer, intervention with high doses of beta-carotene have not so far been shown to be protective, in smokers or in asbestos workers at very high risk of lung cancer. Researchers involved in these studies and experts at the National Cancer Institute have emphasized that the negative findings with high-dose beta-carotene should not in any way deter people from eating fruits and vegetables rich in beta-carotene and should not be taken to undermine the antioxidant hypothesis of disease prevention.

While the effort to understand the current data on beta-carotene continues, we chose for simplicity's sake to focus the Pracon study on vitamin C and vitamin E. We used published research studies to estimate the population preventable fraction for each disease condition, for each nutrient.

For vitamin E and heart disease, the calculations were based on the findings of two major studies from Harvard showing significantly less risk of heart disease in people who used vitamin E supplements. The subjects of the study were more than 40,000 male health professionals and about 80,000 nurses involved in an extensive epidemiological study. The average amount of vitamin E consumed by the top quintile was 400 IU for the men and 200 IU for the nurses. (See references in Attachment 1.)

In the study on male health professionals, the relative risk of heart disease in the highest vitamin E intake quintile was 0.59. In the second quintile, it was 0.74. The bottom quintile of intake was set at a relative risk of 1.0. Using the relative risk figures for each quintile, we calculated the fraction of heart disease that could be prevented if the entire population consumed the amount of vitamin E intake observed in the top quintile (the quintile that experienced the greatest reduction in heart disease risk). In this particular case, we calculated that the preventable fraction of heart disease was 26%, related to optimizing vitamin E intakes. (See Attachment 2 for the method of calculating this value). Translating this level of disease prevention into economic terms, we estimated that, if 26% of heart disease could be prevented in this fashion, there would be 525,000 fewer hospitalizations per year for heart disease, with an annual savings of about $8 billion in health care costs related solely to hospitalization (not including other costs).

New data continue to support the benefits of vitamin E supplementation in reducing the damaging effects of heart disease, not only in the general healthy population but in people who already have confirmed heart disease. An article published in *Lancet* at the end of March reported that vitamin E supplements (800 or 400 IU per day) in approximately 1,000 men with

confirmed heart disease reduced their risk of a non-fatal MI by about 75%, compared to a similar number of men who were given a placebo. (See reference in Attachment 1.)

Similar data for vitamin C and stomach cancer were analyzed. In this case, the calculations were based on the results of five epidemiological studies of vitamin C intake and risk of stomach cancer. (See references in Attachment 1.) The five studies utilized were all case-control studies: two in Italy, one in Germany, one in Sweden, and one in the United States.

For stomach cancer, we estimated that 30% of stomach cancer was potentially preventable in the total population, if everyone obtained an optimal amount of vitamin C. This would save 7,000 hospitalizations annually, for a health care cost savings of $161 million each year. For cataracts, we relied on review articles written by experts in the field of cataract prevention, who estimated that preventing or delaying cataracts for a period of about 10 years could avoid 50% of cataract operations in the elderly. (See reference in Attachment 1.) This would mean avoiding 13,000 cataract operations every year, for a total savings of $49 million annually.

These data on health care cost savings, although admittedly somewhat simplistic, have been very helpful in illustrating the magnitude of the benefits that could be obtained if preventive nutrition were optimally applied. We presented these data in legislative hearings in support of the Dietary Supplement Health and Education Act, which was passed by Congress in October of 1994. The legislation had two primary goals: to assure continued access to dietary supplement products, and to increase access to information about the benefits of dietary supplements.

The first section of the Dietary Supplement Health and Education Act includes fifteen "findings" relating to the safety and benefits of dietary supplements. One of the findings specifically refers to the data we submitted regarding health care cost savings. This Congressional finding asserts that "preventive health measures, including education, good nutrition, and appropriate use of safe nutritional supplements will limit the incidence of chronic diseases and reduce long-term health care expenditures."

Although the Pracon study was relatively small study, we believe it made a major contribution to the Congressional understanding of the potential role of dietary supplements in promoting health and preventing disease. We initially released the findings of the Pracon study at an Annual Conference of the Council for Responsible Nutrition, and we have been continuously surprised at the strong media interest in this study. Also, we know that the results of the Pracon study have inspired at least one other group to sponsor a similar but more comprehensive study. I cannot provide any more details about that study, except to say that it should be published before the end of this year. The Pracon study has also been submitted for publication.

Obviously, major epidemiological studies — even without an accompanying economic analysis — have a great impact on consumer understanding of the importance of good nutrition, and also have a great impact on public health policy. However, it appears that sometimes a study can have even greater influence if an effort is made to quantify the benefits of a particular product or health habit on the incidence of disease, the number of deaths from that disease, and ultimately the cost to society. The Pracon study is one example of an effort to quantify the benefits of optimizing the intake of antioxidant vitamins.

I would now like to take a few minutes to review the provisions of the Dietary Supplement Health and Education Act of 1994 (DSHEA), which established the current groundrules for dietary supplement regulation in the U.S. The new Act assures access to dietary supplement products by declaring that in general dietary supplements are to be regulated as foods and not as drugs. The Act also removes dietary supplement ingredients from classification as food additives, and establishes separate safety provisions for dietary supplements.

DSHEA increases consumer access to information about dietary supplements by permitting a new class of claims called "nutritional support" claims, and by permitting the distribution of certain literature at the point of sale. The literature must be truthful and not misleading, and must be generic and not promote any particular product or company. The industry had hoped that DSHEA would make some changes in the groundrules for health claims, but Congress was unable to agree on such changes.

The new class of "nutritional support" claims permitted for dietary supplements includes four specific types of claims:

(1) claims that a dietary ingredient affects the structure or function of the body;

(2) claims about the biochemical mechanism by which a dietary supplement affects the structure or function of the body;

(3) claims relating to nutritional deficiencies; and

(4) claims about general well-being.

In order to make a nutritional support claim, a manufacturer must have substantiation for the claim, and must notify FDA within 30 days that the claim is being made . Under some conditions, the label of the product may have to include a disclaimer saying:

"This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease."

The conditions requiring the use of the disclaimer are not entirely clear. FDA officials have stated that ordinary statements about the accepted nutritional functions of nutrients can be made freely, both for foods and for

supplements, without any need for notifying FDA or for using the disclaimer. Therefore it is possible that the disclaimer may only be needed when the claim is so closely related to a disease condition that it approaches a "health claim." The practical application of this provision will not become clear until we have had more experience with nutritional support claims. At this time, FDA has received more than 300 notifications about the existence of nutritional support claims, and many of those relate to herbal or botanical products.

Although DSHEA did not make any changes in the current standards and procedures for approving "health claims", it did establish a Commission on Dietary Supplement Labels to review and evaluate all aspects of dietary supplement labeling, and I am pleased to have been appointed as a menber of that Commission. The Commission is especially directed to evaluate the current regulations regarding health claims and to evaluate the appropriate use of nutritional support claims and the use of literature at the point of sale.

DSHEA required that President Clinton appoint a Commission made up of seven members with expertise and experience in dietary supplements. At least three of these were to be scientists, including one with experience in pharmacognosy or related sciences. Dr. Kenneth Fisher, formerly with the Life Sciences Research Office of the Federation of American Societies of Experimental Biology (LSRO/FASEB) was selected as the Executive Director of the Commission. Dr. Malden Nesheim of Cornell University is the Chairman. Both he and Dr. Shiriki Kumanyika of Penn State are nutritionists. Dr. Norman Farnsworth of the University of Illinois is a highly respected pharmacognosist. Margaret Gilhooly of Seton Hall is a food and drug lawyer. I am a nutritionist and a longtime staff member of the Council for Responsible Nutrition, and Robert McCaleb is a biologist and botanist who is President of the Herb Research Foundation. Anthony Podesta is a consultant in public policy.

Under DSHEA, the Commission was to have a lifespan of two years from the date of passage of the Act in October 1994. However, the Commission was not appointed until October of 1995, and did not have its first hearing until February of 1996. It is possible that an extention of time will be requested, for the Commission to complete its work. Four public hearings are scheduled. Two took place in Washington, D.C. , and Salt Lake City, Utah, in February and March of this year. The third is in San Francisco next week (April 26), and the fourth is in Florida early in June. These hearings are opportunities for the public and the industry to let the Commission know what issues need to be addressed, and what recommendations should be considered. All meetings and all documents relating to the Commission are open to the public .

DSHEA also established a new Office of Dietary Supplements at NIH, to conduct and coordinate

research on dietary supplements to compile the results of research, and to advise governmental agencies on issues relating to dietary supplements. The Executive Director of this new office at NIH is Dr. Bernadette Marriott, formerly with the Food and Nutrition Board of the National Academy of Sciences. The first public event sponsored by this new office will be a workshop on "The Role of Dietary Supplements for Physically Active People" on June 3-4 at the National Institutes of Health. We are very hopeful that this new office will serve a valuable role in highlighting exciting new research about dietary supplements and in increasing the amount of research done on dietary supplements.

Because of DSHEA, there is now a very favorable regulatory climate for dietary supplements in the U.S. We believe the U.S. model should be considered by other countries and by international bodies, and we are frankly concerned about the restrictive approaches to dietary supplements taken in some European countries. If such restrictive approaches were adopted by an international body such as the EC or the Codex Alimentarius, there could be serious detrimental effects on international trade. CRN has submitted extensive comments on the currently proposed Codex Alimentarius guideline on dietary supplements, which we believe is much too restrictive.

The U.S. dietary supplement industry foresees a very strong future, with excellent potential for growth. Overall, the science continues to be very positive and continues to point to a great potential for dietary supplements in promoting health and preventing disease. The shock waves sent out by the occasional negative finding shows just how accustomed we have become to a continuing stream of positive information about nutrients and supplements. We see the strong consumer interest in dietary supplements now expanding to include herbal and botanical products as well as the traditional vitamin and mineral products. This strong consumer interest combined with the continued evolution of strong scientific support for the benefits of supplements can be expected to result in longterm growth for the industry.

Thank you very much for your attention.

References Attachment 1

VITAMIN E AND HEART DISEASE

Rimm EB, Stampfer MJ, Ascherio A, et al.
Vitamin E consumption and the risk of coronary heart disease in men. NEJM 1993; 328:1450-1456.

Epidemiological study involving 39,910 U.S. male health professionals, followed up since 1986. The men in the top quintile of vitamin E intake had a relative risk for heart disease of 0.59, compared to 1.0 for the lowest quintile of vitamin E. (About a 40% decrease in risk). The top quintile was composed entirely of vitamin E supplement users, with a median intake of 400 IU.

Stampfer MJ, Hennekens CH, Manson JE, et al.
Vitamin E consumption and the risk of coronary disease in women. NEJM 1993; 328:1444-1449.

Epidemiological study involving 87,245 female nurses, followed up since 1980. The women in the top quintile of vitamin E intake had a relative risk for heart disease of 0.59, compared to 1.0 for the lowest quintile of vitamin E. (About a 40% decrease in risk). The top quintile was composed entirely of vitamin E supplement users, with a median intake of 200 IU.

NEW STUDY ON VITAMIN E AND HEART DISEASE
(not use in economic analysis.)

Stephens NG, Parsons A, Schofield PM, et al.
Randomised controlled trial of vitamin E in patients with coronary disease: Cambridge Heart Antioxidant Study (CHAOS). Lancet 1996; 347:781-786.

Double blind, placebo-controlled study involving 2,002 patients with angiographically proven atherosclerosis, followed for a median of 510 days. Over 1,000 patients (1,035) given 800 IU or 400 IU of vitamin E daily; 967 given placebo. Vitamin E group had a relative risk of 0.53 for cardiovascular death or non-fatal myocardial infarction, compared to placebo group. Reduction in risk was entirely attributable to reduction in non-fatal MI. Relative risk for this endpoint was 0.23 for the vitamin E group, compared to the placebo group.

VITAMIN C AND STOMACH CANCER

Boeing H, Frentzel-Beyme R, Berger M, et al.
Case-control study on stomach cancer in Germany. Int J Cancer 1991; 47:858-864.

Case-control study in 143 cases and 579 controls in Germany. Only vitamin C was protective, after adjustment for other food constituents. Citrus fruit, raw vegetables, cheese (!), and whole-meal bread also associated with decreased risk.

La Vecchia C, Ferraroni M, D'Avanzo B, Decarli A, Franceschi S.
Selected micronutrient intake and the risk of gastric cancer. Cancer Epidemiology, Biomarkers and Prevention 1994; 3:393-398.

Case-control study in Italy with 723 cases and 2,024 controls. Most protective effect from beta-carotene and vitamin C.

La Vecchia C, Negri E, Decarli A, D'Avanzo B, Galloti L, Gentile A, Franceschi S.
A case-control study of diet and gastric cancer in northern Italy. Int J Cancer 1987; 40;484-489.

Case-control study in northern Italy on 206 cases and 474 controls. Green vegetables were protective. Vitamin C and beta-carotene intakes strongly related to decreased risk. Association of individual nutrients not significant when food sources were simultaneously included in the analysis.

Hansson LE, Nyren O, Bergstrom R, Wolk A, Lindgren A, Baron J, Adami HO.
Nutrients and gastric cancer risk: a population-based case-control study in Sweden. Int J Cancer 1994; 57:638-644.

Case-control of 338 cases and 679 controls in Sweden. Strong protective effect of vitamin C and beta-carotene. Also, supplementation with vitamins halved risk after adjustment for dietary intake.

Correa P, Fontham E, Pickle LW, Chen V, Lin Y, Haenszel W.
Dietary determinants of gastric cancer in south Louisiana inhabitants. J Natl Cancer Inst 1985; 75:645-654.

Case-control study with 391 cases and an equal number of controls, in Louisiana. Strong protective effects for fruits and for vitamin C in both blacks and whites.

ANTIOXIDANT VITAMINS AND CATARACT

Taylor A.
Role of nutrients in delaying cataracts. Ann NY Acad Sci 1992; 669:111-123.

In a review of the literature on antioxidant nutrients and cataracts, Taylor estimates that as much as 50 percent of cataract extractions and associated costs could be saved by preventing or delaying cataract development by about ten years in the elderly, since the prevalence of cataract development increases dramatically with age.

Attachment 2

SAMPLE CALCULATION

Sample calculation of population preventable fraction for heart disease, relating to optimizing intakes of vitamin E. Based on Relative Risks reported by Rimm et al in 1993. (See Attachment 1 for reference.)

	QUINTILE				
	1	2	3	4	5
Relative risk as reported	1.0	.88	.77	.74	.59
RR with top quintile equal to 1.0	1.69	1.49	1.31	1.25	1.0

Calculation of preventable fraction:

$$PF = \frac{\sum_{i=1}^{k} P_i \, (RR_i - 1)}{1 + \sum_{i=1}^{k} P_i \, (RR_i - 1)}$$

$$PF = \frac{.2(.69) + .2(.49) + .2(.31) + .2(.25) + .2(0)}{1.0 + .2(.69) + .2(.49) + .2(.31) + .2(.25) + .2(0)} = 0.26$$

CAPSUGEL®

Antioxidants: medicines or food supplements?

By Josef Hasslberger
President of Technical Commission EHPM
Paris, April 1996

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Abstract

The distinction between medicines and food supplements is not facilitated by current European legislation. Medicinal specialities are defined in Directive 65/65 in a very wide way. No corresponding definition for foods or food supplements can be found in EU legislation.

One can search a dividing line based on the kind of substance involved or on the purpose of the product. Both approaches are problematic. Historically, the prevention of illness, that is, the maintenance of good health, has never been an exclusive of medicine.

The question (Medicines or Food supplements?) is not answered with a simple either/or.

Some antioxidants may be foods and medicines, depending on the form of presentation. Some may be only medicines because of a clearly non-food nature of the substance, and some of them may be only foods, at least until such time as sufficient research indicates an application compatible with disease-specific indications.

Although classification is legally and politically interesting, ease of availability to the public may turn out to be — especially in this field of antioxidants — of far greater importance.

What are food supplements?

We do not need to ask what are medicines, they are defined in European Directive 65/65. But there is some doubt as to what really are food supplements, at least if we want to look at the question from a European perspective.

There are a wide variety of traditions within the EU's member countries towards food supplements. A relatively liberal approach is taken in such countries as the UK and the Netherlands. Others, such as Germany, Italy and Greece, consider vitamin products to be medicines if they exceed low dosage limits.

Food supplements are, for much of continental Europe, a relatively new concept. They do not have historical roots. However, the forces of the market are bringing about a gradual elimination of these historical differences.

In general, laws and administrative practices follow changes in customs and practices of the population, not vice versa. Future national and European regulations for food supplements will have to take this into account. They will have to follow the changes in consumption patterns that have come about in the last two decades in this area.

There is considerable growth in the supplements market. One reason for this is that nutrition is being

recognised as a valid tool for maintaining good health. An example is the European Council resolution of 27 May 1993 on future action in the field of public health. It identifies the general objective for future co-operation and community action. One of the aims is a high level of health protection through preventive measures. The resolution says that this is to be achieved by:

- “adding years to life: increasing life expectancy and reducing the incidence of premature death, as well as

- adding life to years: increasing the number of years that can be lived free of illnesses, reducing or limiting the negative consequences of illnesses and handicaps, promoting healthy lifestyles and a healthy physical and social environment, and improving the quality of life in general."

Another example is a recommendation of the Council of Europe, issued in 1994. It urges governments to promote research and information regarding diet and health. The term "preventive nutrition" has been used in this context by the Council of Europe.

There are large potential savings in health care expenditures achievable through good nutrition. The Council of Europe report states that in Germany, the cost of nutrition-dependent diseases in 1988 was estimated to be 42,000 million Deutschmarks.

Dr. Dickinson, will be telling you about the situation in the USA. Billions of Dollars annually could be saved through reduced hospitalisation if Americans consumed optimal levels of the antioxidant vitamins C, E and beta-carotene.

Definitions

The Dietary Supplement Health and Education Act of 1994, in the USA defines food supplements (they are called dietary supplements in the US), in the following way:

“The term 'dietary supplements'-

(1) means a product (other than tobacco) intended to supplement the diet that bears or contains one or more of the following dietary ingredients:

(A) a vitamin; (B) a mineral;

(C) an herb or other botanical; (D) an amino acid;

(E) a dietary substance for use by man to supplement the diet by increasing the total dietary intake; or

(F) a concentrate, metabolite, constituent, extract, or combination of any ingredient described in clause (A), (B), (C), (D), or (E), ...”

The European Federation of Associations of Health Product Manufacturers (EHPM) defines food supplements in the following way:

"Preparations, including tablets, capsules, powders and liquids which are composed of, or contain, nutrients, micro nutrients and/or other edible

substances, consumed in unit quantities and which are consumed in addition to the normal food intake."

Food supplements are intended to provide certain substances that are not easily obtained in sufficient quantity with the normal diet. The rationale of supplementation is simple. When we supply certain substances in greater amounts than contained in a normal varied diet, they may have health benefits by increasing the general resistance of the body. Antioxidants are an example of this.

Categorising food supplements is a difficult task facing legislators, especially in view of the fact that current views differ widely from country to country. The existing legal categories are medicines, dietetic foods and normal foods.

Medicines are defined in Council Directive 65/65/EEC as *"any substance or combination of substances presented for treating or preventing disease in human beings or animals"* and *"any substance or combination of substances which may be administered to human beings or animals with a view to making a medical diagnosis or to restoring, correcting or modifying physiological function..."*

This definition has by necessity been kept very wide. It was made as part of a directive to regulate "medicinal specialities". It was to include all those products that can possibly be considered medicinal. Its purpose was not to establish the border line between foods and medicines.

Dietetic foods are called foodstuffs for particular nutritional uses by Council Directive 89/398/EEC. They are defined as *"foodstuffs which, owing to their special composition, are suitable for their claimed nutritional purpose and are marketed in such a way as to indicate such suitability."*

The term "particular nutritional uses" is then linked to persons whose digestive process or metabolism are disturbed and to certain categories of persons who are in a special physiological condition, as well as small children and infants. Thus we see dietetic foods are directed towards a specifically defined and restricted part of the population, not to all consumers whithout distinction.

For a definition of normal foods, we may quote a definition proposed by Codex Alimentarius. This was published in Codex-Stan 1-1985 and is contained in WHO Glossary 1993: *"Foods are processed and non-processed substances intended for human nutrition and serving to meet the nutritional and energy requirements for maintaining life, growth, and fitness for work and business."*

A similar definition has been elaborated by the EHPM. It is a bit more articulated, defining food as:

"any substance or liquid whether processed, semi-processed or raw, assumed for the purpose of:

- restoring, maintaining or enhancing the body's energy level,

- providing nutrients and other substances useful for correct metabolic function, growth and repair, and/or

- providing pleasure by way of its organoleptic properties.

How will supplements be categorised?

The legislative trend is, to consider food supplements being part of the broad category of foods, not that of medicinal products. This has been indicated by the European Commission. Codex Alimentarius has said so and also the recent US law makes that point quite clear.

One question remains to be answered in this context. Could high dose vitamin preparations be categorised as medicines while low dose vitamin preparations are food supplements? Some national authorities are proposing to do this.

This approach seems attractive at first. It provides a seemingly simple dividing line between the categories. But on closer examination, the definition of high dose and low dose presents problems of legal, practical and scientific nature.

One might refer to RDAs, recommended allowances or reference intakes. But we must consider that food supplements, and especially antioxidants, are not primarily directed to the elimination of deficiency diseases. In present-day nutrition other factors have come into play. For example resistance to stress and extension of useful life span. This new concept of positive health is quite different from the philosophy that inspired RDAs. Dosages that have a preventive effect are often much higher than the RDA would suggest.

It seems unreasonable and almost discriminating to establish maximum dosages of vitamins and minerals. Especially if we are linking them to the amounts that are indispensable for the avoidance of deficiency disease. We would limit paradoxically only the dosage of those substances, that have been found to be indispensable, leaving all the others to the discretion of the manufacturer.

The European Court of Justice has examined the legal side of the problem in its decision of 30 November 1983, in a case against Leendert Van Bennekom. This decision has in part been superseded by legislative developments (the Dutch parliament has passed a law liberalising the sale of vitamins without regard to dosage, except for vitamins A and D. But it is still interesting to examine the Court's verdict.

In it's reasoning the Court analyses the difficulties of an approach based on dosage, stating that *"it is impossible in the present state of scientific knowledge to state whether the criterion of concentration alone is always sufficient in order to be able to determine whether a vitamin preparation constitutes a medicinal product; still less therefore is it possible to specify the*

level of concentration above which such a vitamin preparation would fall within the Community definition of a medicinal product."

Food supplements, like all other foods, should be subject to the principle that at normal levels of consumption there may not be any toxic effects. In this way they are different from medicines. Toxicity is tolerated, as long as the risk/benefit ratio is favourable. But this principle of absence of toxic effects must be strictly connected to the concept of normal levels of consumption. Indeed almost anything may be toxic if consumed in excess.

It is true that vitamins and minerals are needed in relatively small doses. Adverse effects, where they exist, are evident equally at a relatively small dose. For this reason, the EHPM has developed a proposal to satisfy the food safety criterium for supplements, whithout sacrificing availability. A review of published literature was done by Dr. Derek Shrimpton. It is based on the premise that micro nutrients (vitamins and minerals) should be allowed to be consumed in any dose for which no adverse effect has been reported in peer reviewed scientific literature or in responsibly monitored practice. The study lists the levels of intake of vitamins and minerals, at which there should be no safety concerns according to current scientific knowledge.

Preventive nutrition

Food supplements and especially antioxidants are not only consumed to satisfy nutritional and energy requirements. They activate and optimise the human metabolism, with a view also towards prevention of disease. This does not take us into the field of medicine. Even normal foods — we have an example in the healthy mediterranean diet — have preventive properties.

What probably needs to be revised is the extensive interpretation of Directive 65/65. This interpretation leads to the perception that anything even remotely connected with disease must be medicinal.

Possibly the problem can be solved by the establishment of a new category of products in European law that could be called health products. This would be the equivalent of the American dietary supplements. It would be broadly based in the food area. The point of distinction from food would be the possibility to link such health products with actual health benefits, even with preventive properties, and to inform the consumer about these.

Now we still need to answer the question, whether antioxidants are medicines or food supplements.The answer cannot be based only on the kind of substance or on the concentration. We must consider product purpose and presentation. In this sense, an antioxidant can be a medicine, where medicinal efficacy can be demonstrated and where the product is formulated and registered as a medecine.

In many cases however, a producer may not wish to go into the complications of medicinal registration. Or he may not be able to do so, because efficacy against specific disease has not been scientifically demonstrated. In this case, the product will be a food supplement. It will have to follow whatever regulations eventually are going to be made for the supplement category.

Classification is certainly an interesting problem, legally and politically. But ease of availability to the public could be of far greater importance if we wish to fully utilize the potential health benefits of nutrition.

Summary

I would like to put together for you now the most important points made in this presentation.

1) Food supplements, legally, are closer to foods than they are to medicines.

2) One of the important principles for foods is the absence of toxic effects. Therefore any dosage limitations should be based on this principle.

3) Foods can have disease preventive properties

4) One might envision a special category for health products to be established. This would be inbetween the two large categories - foods and medicines.

5) Antioxidants may be foods (food supplements) or medicines, depending on the presentation of the product. It is not the substance that makes the difference, but the intention behind the product as expressed in product presentation.

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Antioxidant nutrients in human disease prevention

By Anthony T. Diplock,
Free Radical Research Group,
Division of Biochemistry and Molecular Biology,
United Medical and Dental School, Guy's Hospital
Paris, April 1996

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Antioxidant nutrients in human disease prevention

By Anthony T. Diplock, Free Radical Research Group, Division of Biochemistry and Molecular Biology, United Medical and Dental School, Guy's Hospital, London SE1 9RT, UK.

Paris, April 1996

Abstract

Intensive research during the past 15 years in many parts of the world has been concerned with the possibility that antioxidant nutrients may have a major role to play in the prevention of several diseases. These include cardiovascular disease, some forms of cancer, and several other disorders many of which are aged-related. Free radicals, which are often highly reactive chemicals, are produced naturally in the body as products of the metabolism of oxygen, and may attack DNA, proteins and lipids in cells in specific ways. The resultant structural disorder is considered to lie at the root of the causation of pathological changes that lead to disease. Prevention of these changes depends on a range of dietary substances, which work together in concert to keep the disease-promoting effects of oxygen radicals in check. The antioxidant nutrients of particular interest are vitamins C and E, the carotenoids, and the trace mineral selenium; added to these are a number of antioxidants, such as flavonoids, which are not nutrients but which may contribute to the antioxidant properties of food.

With regard to cardiovascular disease, there is considerable epidemiological evidence that a low risk of disease is associated with high intakes of antioxidants particularly vitamin E and ß-carotene, and there is an excellent rationale at the fundamental level which can explain the role of oxidative mechanisms, and their modulation by antioxidants, in the process of atherosclerosis which occurs in coronary blood vessels and which predisposes the individual to ischaemic heart disease and coronary infarction. With respect to cancer in certain sites, there is overwhelming evidence that the risk of cancer is very significantly lower in subjects with a high intake of fresh fruit and vegetables. It cannot be said with certainty that this is only due to the high content in these foods of antioxidants and other factors certainly play a part. However there is evidence which shows that, in at least 15 well conducted studies, the blood level of ß-carotene is negatively correlated with incidence of lung cancer, and other cancer sites can be discussed in a similar way. The recent ATBC study in Finland, in which a condition of entry of the subjects to the study was a history of 30 years smoking 20 cigarettes per day, showed an apparent 18% increase in the incidence of lung cancer in the sujects given ß- carotene. Interpretation of this study is difficult but it must be viewed in the light of the very large amount of

evidence of a benefical effect of carotenoids in lung cancer prevention.

The principle present strategy is to obtain evidence as to what is the optimal intake of antioxidant nutrients that may be associated with a low incidence of disease. It is clear that environmental pollutants, which provide sources of free radicals, must be considered as the most damaging variable in assessing the likely impact of these species on disease and antioxidant requirement. There is considerable evidence that antioxidants, which are natural nutrients, are entirely safe and free from undesirable side-effects, and that there is no hazard likely from increasing their level of intake within sensible boundaries. Whether this can be done by dietary means alone is a point of debate at present, and the possibility of encouraging the use of dietary supplements, or of fortifying foods with these nutrients, must be borne in mind.

Lecture

Free radicals, which are atoms or molecules with an unpaired electron, have been implicated in the causation of a number of human degenerative diseases. Among these are cardiovascular disease, certain forms of cancer, and cataract formation. The high reactivity of many free radicals, which are derived as normal products from molecular oxygen during respiration, renders them potentially dangerous if there are not rigorously controlled in a biological environment where they may attack DNA, proteins and unsaturated fatty acids. The resultant structural disorder is considered to lie at the root of the causation of pathological changes that lead to disease.

Prevention of these diseases depends on a range of substances that function together and in an interactive manner. It is thus not possible to single out any single protective factor for study because the function of each depends on others that, like the instruments of an orchestra, together play the tune of protection against disease. In considering disease causation, the primary free radicals that attack intracellular macromolecules are derived from molecular oxygen. The process of respiration, normally regarded as benign and life-giving, as a darker side; respiration is in essence the reduction of oxygen to water, a process that involves the addition of four electrons and four protons to the oxygen molecule. Intermediates in this process are free radicals and other products which, under the influence of free intracellular iron, produce another highly damaging toxic oxygen radical species called the hydroxyl radical. It is this highly reactive molecule that is thought to be the primary damaging agent that causes, at first subtle, and then more wide-spread, pathological changes which cause disease.

The control of these degenerative processes is carried out by a network of agents that either prevent the primary formation of hydroxyl radicals or are responsible for limiting the secondary damage they cause. The primary effects are limited and controlled by a range of enzymes which contain, and depend upon for their function, mineral elements. These elements are manganese, copper and zinc, and selenium. It follows that restriction, by limited dietary intake of these elements, may be important in disease causation or, put the other way, it is necessary to ensure adequate amounts of these elements in the diet to ensure adequately functional enzymes which prevent the formation of primary radicals.

The prevention of the proliferation of secondary radicals is carried out by vitamin E, vitamin C; ß-carotene may have a similar function. These three nutrients work together to quench secondary radicals as soon as they are formed following attack by primary radicals on intracellular macromolecules. Further damage limitation is affected by selenium, working within enzyme structures, so that metabolites that

may cause further free radical damage are eliminated before they can cause harm.

It will be seen that the protective agents in this sophisticated network of free radical control are all nutrients, and hence the name 'antioxidant nutrients' has come into usage to describe them, because they antagonise processes that involve oxidation. There is now considerable evidence to show that free radical events are involved in the complex processes, which occur over many years, which lead to atherosclerosis, the loss of arterial elasticity that causes ischaemic coronary artery disease (heart attack) and ischaemic cerebral artery disease (stroke). Furthermore, free radicals are certainly involved in many of the complex events, also extending over a long periode of time, that lead to cancer. Cataract formation is also best explained by free radical mechanisms which have also been implicated in the causation of several other serious diseases. There is excellent experimental evidence that these processes can cause disease and, more importantly in the present context, that the antioxidant nutrients may have a vitally important role to play in disease prevention.

The above evidence, which is of course some distance from true life involvement in acute human disease, is only part of the compelling case that can now be made for supposing that the antioxidant nutrients may be of key importance in preventing such socioeconomically important diseases as heart attack, stroke, and some forms of cancer. There now exists a huge databank of epidemiological evidence which supports the thesis; for example the large WHO/Monica European cross-cultural study demonstrated conclusively that the well-established gradient in ischaemic heart disease mortality from North to South in Europe was correlated with a high degree of statistical significance with blood levels of antioxidants, particularly vitamin E. Similarly, in a study in Edinburgh, there was a high statistical correlation between a low blood level of vitamin E and high incidence of angina. Results from the Harvard Physicians' and Nurses' Studies have revealed up to 45% reduction in heart disease in those subjects who were taking a dietary supplement of 100mg vitamin E (or more) per day. The very recent publication of the results of a placebo-controlled, double-blind study in Cambridge, England has shown that daily supplementation with large amounts (250-500mg) of vitamin E for an average 510 days resulted in a 77% reduction in heart attacks in patients who had angiographically proven coronary arteriosclerosis. These are but a few of many convincing studies worldwide that all point in the same direction; few studies, if any, demonstrate a lack of such correlations.

With respect to cancer in a number of different sites, a very large body of evidence demonstrates the prophylactic effect of diets containing high amounts of fresh fruit and vegetables. It is likely that the content of vitamin E and C, and carotenoids are the major factors that afford this protection (and indeed some studies demonstrate this conclusively) but other constituents

of these foods are also considered to be important. Similar convincing results have been obtained in cataract with respect to the preventive effects of vitamin E and carotenoids.

The case for promoting a high dietary intake of the antioxidant nutrients is now so compelling, that the urgent questions need to be answered as to amount of these nutrients that are needed for disease prevention. Although no categorical answer can be given to this question at present, it is possible to make some estimates. If one studies the blood levels of individuals who are in the lowest category (quintile) of disease risk in the epidemiological studies, there is remarkable constancy in them in populations of widely differing ethnic and cultural origin. One can then ask the question: how much of each of the nutrients vitamin E, vitamin C and ß-carotene is needed daily to achieve the steady state blood level of the lowest risk quintile? Again, although no categorical answer can be given, the following figures are approximations that can give some indication of what may be required: vitamin E, 40-50mg/day; vitamin C, 100-150mg/day; ß-carotene, 2-10mg/day. These values for vitamin E and C are respectively four times, and three times the USA RDA. They are thus not 'mega' doses by any means. It should be emphasised that these are not recommendations for the general public but are given as indicators only. Much more work is needed before any recommendations can be formulated.

It would be difficult or impossible to achieve these levels of intake through diet alone and it is considered at the present time that it might be necessary to encourage individuals to take a modest supplement of these nutrients in order to achieve the desired level of intake. An alternative is that, if the health benefits of antioxidant nutrients become established, it may be desirable to consider fortification of some foods with these nutrients. It can be categorically stated that the safety of such a recommendation can be guaranteed. There is ample detailed literature, including double blinded clinical studies, which demonstrates without any doubt that, taking doses many times larger than those suggested, is completely safe. The only caution must be for vitamin E which may cause some problems at very high levels of dosage in patients on anticoagulant therapy or who have marginal vitamin K deficiency caused by malabsorptive difficulties. Furthermore, in the light of recent findings of higher rates of lung cancer in heavy smokers taking large supplements of ß-carotene, large increases in intake of this nutrient should be avoided.

The possible benefit to Health Budgets of following the information given here cannot be overestimated. The free availability of sources of these nutrients, without recourse to medical advice, is therefore considered to be of the greatest importance.

CAPSUGEL®

Roundtable discussion synthesis

By Maurice Hanssen, Chairman
Director of the European Health Products Manufacturers Association
Paris, April 1996

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Introduction by Mr Hanssen

Regarding health food supplements, and especially vitamins and antioxidants, the question is to find a way forward for Europe. The trend in Europe is the opposite of the FDA's policy as described by Ms Dickinson earlier in the morning. What should be expected is that when products are safe and well-balanced, honest information should be allowed. But health claims are strictly forbidden in Europe, which is a disastrous situation. Why are we barred from telling the truth? There is no logic in this, when one considers that salt, for example, should be limited as well due to its negative effect on health when consumed in excessive quantities.

So why not move to new concepts? The DG3 at the European Commission is examining the legal situation regarding health food supplements — including herbs which are not directly covered by this symposium. In that respect, what is going to happen with the Codex Alimentarius is a tough issue that health food professionals should look at carefully. One recommendation here would be to sort out what we want from scientists and advisers. The best bet would be to clarify what should and could be made available to the public in answer to its demand for more information about nutritional matters.

Mr Torgerson (University of York): The economic aspects of ATBCE/beta-carotene show that it is possible to increase their positive effects while decreasing health costs.

Numerous cases of angina have been avoided thanks to Vitamin E, with evidence of a better quality of life for patients. In conclusion, Vitamin E is beneficial when calcium, for instance, is not.

Dr Cahane (Doctor): Prevention is the key word. We have to take care of the diseases before they appear. Debate concerns the dosage evaluation of antioxidants and the length of intake, which is generally long. Nevertheless, the best solution in the long term is healthy eating along with antioxidant supplements. Doctors have to supplement their patients in this respect when symptoms such as weight, skin or hair problems become apparent.

Mr de Winter (BEUC), referring to the ATBC study published in The Lancet, stresses that the scientific position on this matter is not fully consistent, and insists that it will take years for the debate to be settled.

Dr Dickinson: I totally agree with the previous conclusion: supplements are no substitute for healthy eating.

Pr. Diplock: To make a comment about the Finn study, antioxidants do not play a part in phase 2 or 3 of a cancer, but evidence of their positive effect has been shown in phase 1.

Questions

Dr Tissot (CH): A good example of lack of information is Vitamin C, which has a reputation for preventing people from sleeping at night. If information only lies in the hands of health professionals, how are they going to deal with this increasing need for information from the public?

Mr Hanssen: This should be a European decision. But here again the principle of subsidiarity is at stake. Brussels ensures a consistent structure, although the individual nations make their own laws. The advice here is to turn to your government.

In the Netherlands, for claims, the borderline between health food and medicines is strictly drawn. In France, there is a powerful lobby from pharmacists against direct information. Over the past few years, things have been changing in the UK and English-speaking countries where doctors have a better understanding of the context and the needs involved. The hope is that this will help other countries such as France and Germany to move to new concepts as well. There is a need to educate people.

Mr Hasslberger: There is an interesting report by Lannoye from Belgium on alternative medicines. This report to the European Parliament moves toward taking alternative medicine into consideration.

Another aspect that needs to be understood is the importance of the Codex Alimentarius in the field of health food supplement regulations. Though each country will promote its own view in this commission, the law will be passed by a majority vote. It is the responsibility of manufacturers and EHPM members in each country to take advantage of this opportunity.

Pr. Diplock: In favour of giving more information to the community of doctors. We need to look at the whole picture, not each individual study, to see evidence of effects. Doctors are the link with patients: they need more information to cater for this need.

Dr Cahane: A particular wish that industry would publish more educational information for doctors, for the benefit of patients.

Dr Dickinson: This year the European legislation is going to be approved. It is of great importance that manufacturers should take part in the process.

Pr. Diplock: It is time to resolve to support this change in Europe. It is important not to be satisfied with the current accepted levels.

Mr Zeller (Bop Guide) (DK): Have there been any studies of the local effect of antioxidants?

Pr. Diplock: Not many, but there is certainly work to be done in this field.

Final conclusions

Mr Hasslberger: We need to organise a movement in favour of positive legislation. More liberal regulations are essential to bring together the scientific data. Everyone must contribute and seize the opportunity offered by antioxidants.

Dr Cahane: We have nutritional deficiencies (because of pollution, overconsumption of fat, incorrect cooking, etc.) and we therefore need supplements. Scientists need to get to work to prove the beneficial effects of food complements and promote widespread use of nutriments.

Mr de Winter: The benefits of vitamins E and C will become clear in the future.

Dr Dickinson: Keep a check on product safety —consumers are capable of picking and choosing, and they themselves have opted to take vitamin E. If the products had not been available on the market we would not have been able to carry out these studies. Consumers are a step ahead of our research, and they must have a free choice.

Pr. Diplock: We need to convince legislators that we are not just swimming with a fashionable tide, and that the benefits of certain antioxidants have been scientifically proved. We need to carry out research and studies, and lobbying to obtain funds to finance these studies; we need hard evidence.

Mr Torgerson : The cost of research into antioxidants is not very high, but it does not present any benefits for laboratories. Authorities need to finance research work, and national governments need to step up research investment.

Mr Hanssen: Thank you for this very interesting and intellectually stimulating debate. I have learned that it is possible to change people's way of thinking, and to get governments to take action, but we need to act quickly on the text which is to be adopted this summer by the European Commission.

So, a new awakening or a dark age? The climate is changing everywhere in Europe, and we hope the consumer's voice will be heard in Brussels. We also hope that the American model will expand to Europe. There is a huge demand for quality and honesty. The way to make the industry grow is undoubtedly to carry on producing good, honest products, and to have the right to make this known.

There was unanimous agreement on the need for product quality and safety, more information, and lobbying of governments and authorities for regulations to satisfy each country.