ILSI Europe
Report Series

ANTIOXIDANTS: SCIENTIFIC BASIS, REGULATORY ASPECTS AND INDUSTRY PERSPECTIVES

Summary of a Workshop held in February 1996

Organised by
ILSI Europe
Antioxidant Task Force

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Printed in Belgium

ISBN 1-57881-016-7

Report on Antioxidants: Scientific Basis, Regulatory Aspects and Industry Perspectives

ILSI Europe Antioxidant Task Force, 83 Avenue E. Mounier, B-1200, Belgium

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ANTIOXIDANT TASK FORCE

Antioxidants: Scientific Basis, Regulatory Aspects and Industry Perspectives

ILSI Europe Antioxidant Task Force, 83 Avenue E. Mounier, B-1200, Belgium

ILSI Europe held a 2 day workshop in Brussels, on 8-9 February 1996. This report has three objectives, namely, to provide an account of the 15 presentations given during the course of the first three sessions of the workshop, to highlight key areas that emerged during the discussions of the fourth session and to draw conclusions. The report has been written by Dr. J.C. Stanley (Head, Lipid Metabolism Group, Institute of Food Research, Norwich Laboratory, Colney, Norwich, NR4 7UA UK).

Key words: antioxidants, regulatory framework, product improvement.

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Executive Summary

The objective of the Workshop on Antioxidants: Scientific Basis, Regulatory Aspects and Food Industry Perspectives was to bring together representatives from the food industry, regulatory agencies, academia and consumer groups. It took place 8-9 February 1996 in Brussels and was the third event to be organised by the Antioxidant Task Force. The two previous events were an International Symposium on Antioxidants and Disease Prevention, which resulted in the publication of a concise monograph, and a Workshop on ß-Carotene, Vitamin E, Vitamin C and Quercetin in the Prevention of Degenerative Disease: The Role of Foods, proceedings of which were published as a workshop report.

The February 1996 workshop consisted of four sessions. A scientific overview of antioxidants was presented in the first session. This was followed by sessions on the potential for product improvement and on the regulatory framework for antioxidants. A panel discussion took place in the fourth session. The major focus of the workshop was the so-called natural antioxidants such as vitamin E and vitamin C rather than the synthetic antioxidants such as BHA (butylated hydroxyanisole) and BHT (butylated hydroxytoluene).

Scientific overview on antioxidants: There is good evidence from a variety of experimental approaches that free radicals are involved in processes leading to cancer and cardiovascular disease and that these free radical-mediated events can be modulated by antioxidants. However, methods for measuring free radical-mediated damage to nucleic acids, proteins and polyunsaturated fatty acids in humans *in vivo* need to be refined. The level of intake of antioxidant nutrients desirable for optimal nutrition is still an open question, and there is little information on antioxidant bioavailability *in vivo* in humans. These two areas should be major targets of future research. Although doubling intakes of fruits and vegetables is likely to have important health benefits, the European population remains reluctant to follow such advice. Barriers include tradition, lack of and/or confused knowledge, and issues of availability, quality, cost and convenience of fruits and vegetables. The relationship between antioxidant status and intake is complex. It is important to realise that antioxidants are only one class of plant-derived products with protective properties.

Potential for product improvement: The addition of antioxidants to foods not only is beneficial for health but also plays a role in preventing off-flavour development, discolouration and textural changes. If people will not increase their consumption of fruit and vegetables, supplementation or fortification can be considered. The addition of vitamin E can be used to restore, fortify or enrich oils and fats. In Germany, the fortification of beverages with vitamin C makes a significant contribution to intakes. Although antioxidants are ubiquitous in the plant kingdom, commercial sources are limited and the suitability of an antioxidant for a particular application is difficult to predict. Some consumer organisations consider it undesirable to add antioxidants to foodstuffs not originally containing them. Many links in the food chain could contribute to the optimisation of the antioxidant content of foods including plant breeding, agricultural practice, harvesting practices, raw material selection, processing, storage, transport conditions and cooking practices.

Regulatory framework: There are enormous differences in the fortification policies of member states of the European Union. Harmonisation of legislation in EU member states remains a distant prospect, although a timetable is in place. The key questions will be nutritional need and safety. In the United Kingdom the single criterion for the control of fortification is that the food as sold should be safe. Until recently Sweden had a very liberal attitude toward the addition of vitamin and mineral products, but this is changing. Spanish people eat a Mediterranean diet and, as a result, the addition of nutrients to foods for public health reasons is not a high priority. In the United States, the distinction between foods and drugs is becoming less clear.

The workshop achieved its objective of bringing together representatives of the food industry, regulatory agencies, academia and consumer groups. Such contacts will have to be maintained if scientific knowledge is to be translated effectively into product development in a way that safeguards the interests of the consumer.

Introduction

Dr M Horisberger (Nestec Ltd, Vevey, CH) introduced the workshop by summarising the activities of the International Life Sciences Institute (ILSI) Europe Antioxidant Task Force, outlining the structure of the workshop and highlighting some of the difficulties associated with translating scientific knowledge into product development.

In July 1993 the task force organised an International Symposium on Antioxidants and Disease Prevention in Stockholm which resulted in the publication of a concise monograph. Although this symposium was highly successful as a scientific meeting, it only addressed briefly the practical application of the current state of knowledge on antioxidants. Accordingly, the task force decided to address this issue in a Workshop on ß-Carotene, Vitamin E, Vitamin C and Quercetin in the Prevention of Degenerative Disease: The Role of Foods, which was held in June 1994 in Evian. Although a lot of time was spent debating scientific issues and methodology was a major preoccupation, it was possible to draw some general conclusions, and these were published as a workshop report. After discussing the report, the task force concluded that the next step should be to organize a second workshop bringing together representatives of the food industry, regulatory agencies, academia and consumer groups to examine how existing knowledge on antioxidants could be applied. This workshop was held in Brussels in February 1996.

Because science is the basis of product development, the first session of the workshop will be devoted to a scientific overview of antioxidants. At a time when everything is regulated by budgets there is an unfortunate temptation to cut basic research. Scientists must remind decision makers in industry and elsewhere that there are no shortcuts in science while avoiding the temptation to adopt a wait-and-see attitude. The second session will deal with the potential for antioxidants in product improvement. In discussions in this area, one should “beware of extremes and learn the power of moderation”. In the third session the regulatory framework will be discussed from the perspective of the European Union and individual countries. It should be kept in mind that no food laws would ever be written if all objections had first to be removed. However, although the driving force of science requires the accelerator of marketing, it also needs the brake of legislation to ensure safety. The fourth session will be a panel discussion which will urge that practical conclusions should contribute to the regulatory decision process as well as serve as a basis for product development. Despite recent controversies in antioxidant research, the conclusions drawn from the two previous meetings organised by the task force are still valid. This suggests that ILSI has avoided drawing conclusions prematurely. The eagerness of food industrialists and others to act must be tempered by an appreciation of the imperfections in our scientific knowledge and understanding.

Session 1: Scientific Overview on Antioxidants

Professor A Diplock (Guy's and St Thomas Hospitals, London, UK) gave a presentation entitled "Antioxidant Nutrients in Human Disease Prevention: State of the Art", which reviewed comprehensively the scientific evidence for a role of antioxidants in the prevention of cancer and cardiovascular disease.

Oxygen-derived free radicals attack nucleic acids, proteins and polyunsaturated fatty acids (PUFAs). There is excellent evidence that oxidised low-density lipoprotein (LDL) is a major but not the only player in the process of atherosclerosis leading to coronary heart disease. Minerals (selenium, manganese, copper, zinc) are involved in enzymatic protection mechanisms. Vitamin E and vitamin C, perhaps working together, are involved in free radical scavenging. The role of carotenoids is still uncertain.

Oxygen can accept up to four electrons. The addition of one electron produces a superoxide anion radical which can accept a second electron to produce a peroxyl anion, which will eventually produce hydrogen peroxide. Additional processes are catalyzed by iron, and both the superoxide anion radical and hydrogen peroxide are involved in the generation of the very highly reactive hydroxyl radical, which is particularly damaging to living cells. Attack on a PUFA yields a PUFA radical, which then interacts with oxygen to give a lipid peroxyl radical. Vitamin E quenches the peroxyl radical by donating its labile hydrogen to form a lipid hydroperoxide, and a vitamin E radical is formed. Vitamin E can be regenerated by vitamin C or some other mechanism. When there is a dietary insufficiency of vitamins E and C, the lipid peroxyl radical can attack another PUFA and form a new PUFA radical. This becomes a chain reaction which is highly damaging to living cells.

The atheromatous plaque (deposition of fatty material within the intima of the artery) ruptures during a heart attack, generating a thrombus which completely occludes the artery. Circulating LDL is trapped within the intima of the artery, where its PUFAs undergo free radical attack. The PUFA hydroperoxide is degraded to a range of low-molecular-weight aldehydes which interact with ε amino acid residues of the apolipoprotein to form oxidatively modified LDL. The intimal macrophages recognize oxidatively modified LDL, take it up and turn into foam cells recognisable by their very high lipid content. Foam cells are deposited within the intima leading to the formation of fatty streaks, which are the beginning of the process of plaque formation.

There is a gradient of ischaemic heart disease (IHD) mortality across Europe. Finland (Karelia) and Scotland (Edinburgh, Glasgow) have an incidence of 400-450 per 100,000 men, whereas in Spain (Catalonia) the incidence is about 60. The cross-cultural MONICA study demonstrated a negative correlation between plasma vitamin E levels and incidence of IHD. In the Edinburgh study, the highest levels of plasma vitamin E were associated with the lowest risk of angina pectoris. The male health professionals study in the United States demonstrated that the age-adjusted risk of coronary heart disease (CHD) fell significantly with increasing intakes of vitamin E. Criticisms of this study include the possibility that health-conscious physicians may be taking unrelated measures to safeguard their health for which vitamin E is a marker. The nurses study demonstrated a similar relationship.

Gladys Block reviewed the numerous epidemiologic studies which examined the relationship between the consumption of high levels of fruits and vegetables and the prevention of cancer. She reviewed 156 studies which met rigorous inclusion criteria and examined the relationship between fruit and vegetable intake and a range of different cancers. Beneficial effects were seen in 128 studies. For lung cancer, 24 out of 25 studies showed a beneficial effect where smoking was controlled. It was concluded that major public health benefits could be achieved by substantially increasing the consumption of fruits and vegetables.

The beneficial effects of fresh fruits and vegetables were assumed by many scientific investigators to be due to the antioxidants they contain. In 15 out of 16 studies, high plasma levels of ß-carotene correlated with low incidence of lung cancer (and cervical cancer). In smokers the greater the number of cigarettes smoked, the lower the serum ß-carotene. However, in both studies ß-carotene could be a marker for something else. The ATBC cancer prevention study in Finland studied subjects who were heavy smokers for 36 years and who had probably precancerous lesions on entry. There was a statistically significant 18% higher incidence of lung cancer in subjects given ß-carotene. Exacerbation of lung cancer at a late stage of the disease by ß-carotene cannot be ruled out. Results of the multicentre ß-Carotene and Retinol Efficacy Trial (CARET) were originally communicated at a press conference by the National Cancer Institute of the U. S. National Institutes of Health. The results have now been published in a reputable journal. Heavy smokers and/or asbestos workers, presumably already carrying precancerous lesions, were recruited and received either a combination of 30 mg ß-carotene and 25,000 IU retinol or placebo. The study was terminated early after 4 years because a benefit of the treatment could not be observed and because a 28% increased risk for lung cancer and 17% increased risk for total mortality were observed.

In the Physicians' Health Study, the longest intervention trial with a duration of 12 years of treatment with 50 mg ß-carotene every other day, there was no evidence of either benefit or harm in smokers and non smokers. Supplementation with ß-carotene in the Women's Health Study was discontinued because following the results of the other intervention trials, no benefit from treatment with ß-carotene was expected in this well-nourished group of women.

To summarize, there is good molecular evidence for the involvement of free radicals in processes leading to cancer and cardiovascular disease and for the modulation of these free radical events by antioxidants. Animal models provide some evidence that supports the involvement of free radicals in these processes and their modulation by antioxidants, particularly in relation to cancer. Human epidemiologic evidence also suggests a correlation between antioxidant intakes or serum concentrations and incidence of or mortality from cancer and cardiovascular disease. This is supported by prospective human epidemiologic evidence that links low intake or serum concentration of antioxidants with subsequent elevated risk of disease. There is also some evidence that intervention with these nutrients leads to lower disease risk. However, the level of intake of antioxidant nutrients desirable for optimal nutrition is still an open question.

Professor P Fürst (University of Hohenheim, Stuttgart, D) presented a thorough review of dietary sources of antioxidants, identified the major food contributors of antioxidants in the diets of various European countries and speculated on future trends in fruit and vegetable consumption.

Vegetables, grains and fruits contain small amounts of a huge variety of chemopreventive substances called phytochemicals. Among these are the nutritive antioxidants, including more than 500 carotenoids such as ß-carotene (sweet potatoes, carrots), lutein (kale, spinach), lycopene (tomatoes), the tocopherols (nuts, vegetable oils) of which α-tocopherol is the most active, and vitamin C (citrus fruits and juices), which exists in oxidised and reduced forms. The non nutritive antioxidants include more than 2000 flavonoids such as quercetin, kaempferol, myricetin, apigenin and luteolin, which are commonly found in tea, onions and apples. Red wine is an important source of flavonoids in some populations.

Translating data on food consumption into nutrient intakes is beset with problems, including variations in food composition, inadequate techniques for analysis, under- and overreporting and uncertainties concerning bioavailability. Food frequency techniques are commonly used to gather such data. In the United States two-thirds of recommended intakes can be achieved with only five foods for ß-carotene and with 10 foods for vitamin C, but more than 20 are required for vitamin E.

In Germany, the Netherlands, the United Kingdom, southern Italy and the United States, vitamin C intakes vary between 74 and 114 mg/day, thus fulfilling requirements. In southern Italy carotenoid intakes are high (10-15 mg/day) but are low (1.6-2.7 mg/day) in the United Kingdom. Vitamin E intakes are high in southern Italy, are approximately the RDA in Germany and in the Netherlands, and are very low in the United Kingdom and the United States. This reflects high intakes of fruits, vegetables and vegetable oils in southern Italy and very low intakes in the United Kingdom and the United States.

Doubling intakes of fruits and vegetables to five servings per day is likely to have important health benefits. However, European populations do not seem to understand or want to follow advice to increase their fruit and vegetable consumption. Tradition, lack of and/or confused knowledge, availability, quality and cost are all factors. The scientific community is responsible for some of the confusion.

Professor S Renaud (University of Bordeaux, Bordeaux, F) talked about the relationship between antioxidant status and intake.

The relationship between antioxidant status and intake is not simple and is complicated by absorption, bioavailability and homeostatic mechanisms. Antioxidant status is the balance between pro-oxidant forces and antioxidant mechanisms, which comprise enzymes (superoxide dismutase), low-molecular-weight antioxidants (ubiquinol, uric acid) and dietary antioxidants (vitamin E, vitamin C, ß-carotene, flavonoids). α-Tocopherol in adipose tissue (90% of the body pool) is correlated with dietary intake and plasma concentration, suggesting that plasma concentration is a good way of evaluating α-tocopherol status. Vitamin C ingested as cooked broccoli, orange juice, fruit or in synthetic form is equally bioavailable as determined by plasma levels. Correlation between vitamin E intake and plasma level is not strong, but for vitamin C it is stronger. The use of hormonal contraceptives is associated with lower levels of plasma and platelet antioxidants, leading to increased thrombin-induced platelet aggregation.

In cross country comparisons, cerebrovascular mortality is positively related to vegetable fat consumption owing to its polyunsaturated fat content and inversely related to vegetable consumption. Consumption of the three main sources of antioxidants (vegetables, vegetable fat and fruit) is inversely related to coronary heart disease mortality. However, wine consumption is the variable that is by far the most strongly inversely related to cardiovascular disease mortality whereas consumption of dairy products is positively related. Coronary heart disease mortality in nine Mediterranean cohorts is lower than in the United States and the Netherlands but is higher than in Crete.

Duplication of the Cretan diet (more bread, vegetables, legumes and fish; less meat; no day without fruit; butter and cream replaced by canola oil-based margarine) in an intervention trial on coronary patients led to a 76% reduction in cardiovascular mortality after 27 months, an effect already apparent after 2 months. Plasma vitamin E was 10% higher in the experimental group despite a 10% lower intake. Wine intake was the factor most closely related to plasma vitamin E. Animal experiments suggest that the polyphenols of red wine spare plasma vitamin E by decreasing lipid peroxides and conjugated dienes. Other nutrients may spare vitamin E and improve its status.

Session 2: Potential for Product Improvement

Professor F Escher (Swiss Federal Institute of Technology, Zurich, CH) gave a presentation on the role of antioxidants in food stability, which he illustrated with numerous practical examples.

Food quality comprises physiological factors (nutritional value, wholesomeness), sensory properties (colour, flavour, texture) and socioeconomic factors (availability, convenience, price). Oxidative changes in foods (enzymic and nonenzymic lipid oxidation, polyphenol and ascorbic acid oxidation) affect colour, flavour, nutritional value, wholesomeness and in extreme cases texture. Susceptibility to lipid oxidation is caused by factors intrinsic to the product such as lipid composition, moisture content (which is related to lipid oxidation by a J-shaped curve), physical state (the amorphous state is more stable than the crystalline state), the integrity of compartmentation of plant foods, and extrinsic or environmental factors such as oxygen concentration, light exposure (transparent packaging may be an advantage for marketing but aids the oxidative development of off-flavours) and temperature (although lipid oxidation is less sensitive). In foods processed by conventional methods, susceptibility to lipid oxidation is lowest in canned foods (expulsion of oxygen), intermediate in frozen foods (low temperature dependence) and highest in dried foods (granular structure). Some new foods are extremely susceptible to off-flavour development and discolouration. The warmed-over flavour is a major problem for meat formulations for catering and menu components in sterilized or frozen trays provide convenience at the expense of susceptibility to lipid oxidation.

Strategies for preventing oxidative reactions include physical and chemical methods. Physical methods include retention of structure in plant foods (e.g. slow roasting maintains hazelnut structure), inactivation of oxidative enzymes (blanching), adjustment of moisture content, adjustment of temperature, use of non transparent packaging to reduce light exposure, optimal physical state (achieving the amorphous state in a frozen product can lower oxygen diffusion 10^3- to 10^4-fold) and minimising the initial oxygen concentration. Chemical methods include exploiting the antioxidative potential of ingredients of a food product (rosemary), isolating and using natural antioxidants (rosemary), using synthetic antioxidants (BHT, BHA) and generating antioxidants during processing (Maillard reactions create antioxidative properties but can reduce wholesomeness). Meat formulations in heat-sterilized trays provide a good example of the potential of physical and chemical methods in preventing lipid oxidation. The following all reduce lipid oxidation as judged by ethane production or thiobarbituric acid reactive substances (TBARS): high-temperature, short-time sterilization; packaging in aluminium foil or cartons to prevent light exposure; flushing with nitrogen; and addition of rosemary extract.

Antioxidants are one option for preventing quality losses in food caused by lipid oxidation but are never used in isolation. The addition of antioxidants to foods not only is beneficial for health but also plays a role in preventing off-flavour development, discolouration and textural changes. This is important because food is not bought primarily for its nutritional value but rather for its smell, taste and appearance.

Dr D Richardson (Nestlé UK Ltd, Croydon, UK) gave a wide-ranging presentation on health aspects of antioxidants in foods and the opportunities for the food industry.

Antioxidants play a role in maintaining product quality and consumer health. Product development is driven by the consumer's appetite for healthful product variety and convenience, the government's concern for preventive medicine leading to health care savings, industry's desire for innovation and value-added products, nutritional science's increased understanding of the relationship between diet and health, and food technology's development of new ingredients, processes and packaging. Innovation is occurring throughout the food chain, and consumer expectations now encompass not only food quality but also improved quality of life. The number of new food and drink products increases every year, and 10% of them have healthy-eating statements. Low-fat and low-calorie products top the list, with vitamins appearing high on the list. Vegetarian products and microwavable products constitute an increasing percentage of new products. Consumer perceptions of unhealthy foods focus on fat and of healthy foods on vitamins. Awareness of nutrients in fortified products is greatest for vitamin C, with antioxidants farther down the list. Consumer interest in products is greatest for superstimulants and isotonic drinks and in the longer term for nutritional health care and functional foods. Products which cross the food-pharmaceutical interface will become common.

Research into health-enhancing diets, foods, ingredients and nutrients will include their safety, substantiation of health claims, communication of health benefits and appropriate labelling and marketing, innovative technological advances, and appropriate and secure regulatory frameworks. In the United Kingdom, the antioxidant research programme in the Ministry of Agriculture, Fisheries and Food was created to improve the science base for establishing recommended dietary intakes, to understand the mechanisms which maintain cell and tissue integrity, to explore the roles of free radicals in human disease and to develop sensitive indices of antioxidant status and oxidative stress in humans to help substantiate health claims and statements. The Health of the Nation document, which focused on quantitative reductions in total and saturated fat consumption, presented an opportunity for industry to work with government and academia to develop ways of achieving the targets. The fat audit of products reviewed fat quantity and quality, identified the ingredients contributing the fat, determined the proportion of fat from each ingredient and explored opportunities for fat reduction consistent with taste and functionality. Reduced consumption of total fat and increased consumption of polyunsaturated fat have implications for antioxidants. Culinary aspects such as the loss of vitamin E during frying were also examined. Working groups of the Committee on Medical Aspects of Food Policy (COMA) are reviewing nutrition and health messages and the relationship between diet and cancer.

The message to increase vegetable consumption is a positive message, unlike the majority of previous health messages. Different classes of antioxidants act together synergistically to protect the plant and the consumer. The U.S. Department of Agriculture's food pyramid emphasises the beneficial properties of garlic and cabbage. There is a lot of interest in the antioxidant properties of oats. A survey of foods with medicinal properties, their active principles, their medicinal actions and their indications, emphasises the range of substances that might be involved. How to screen these numerous compounds to know which to focus on is a major problem.

If people will not increase their consumption of fruits and vegetables, supplementation or fortification can be considered. Candidates for fortification include foods for special dietary uses, foods which have lost nutrients during manufacture, margarines, low-fat spreads and staple foods. Criteria to consider include safety, flexibility, labelling and claims. Additionally, upper levels of antioxidant intake are ill-defined in many cases.

Improving the Antioxidant Value of Foods: Three Case Studies

1. Dr L Tijburg (Unilever Research Laboratory, Vlaardingen, NL) gave a presentation entitled "Improvement of the Antioxidant Status of Fat- and Oil-derived Products".

Fats and oils are an important source of tocopherols, tocotrienols, carotenoids and polyphenols. Food companies can increase the antioxidant content of their products by optimal processing of fats and oils or the addition of antioxidants. Processing can be modified to increase the release of antioxidants from oil seeds. Protection from light and oxygen and the use of stainless steel containers to minimise oxidation via free-metal-ion catalysis can maintain antioxidant levels during storage. Conversion of crude oil to purified oil requires degumming, bleaching and high-temperature steam distillation. α-Tocopherol losses of 25–35% are considered acceptable. The addition of vitamin E acetate can be used to restore, fortify or enrich the oil or fat. The addition of micronutrients and nonnutrients to products should be based on sound nutritional and scientific considerations, the levels added should be significant and safety aspects must be considered.

Fats and oils and products derived from them account for 50% of the source of vitamin E intake of the Dutch population. The use of low-fat or very-low-fat products may therefore reduce the intake of vitamin E. When subjects in an intervention trial reduced their fat intakes from 40% to 30% en, vitamin E intakes dropped by 40%. Thus, it makes sense to increase the vitamin E content of low- and very-low-fat products to the level of full-fat products, but this is not allowed in all European countries. Before marketing a product such as a margarine enriched with vitamin E, vitamin C and carotene to about three times the average daily intake, it is necessary to consider its safety, the strength of the scientific evidence for its efficacy, restrictions in existing legislation and the claims that are going to be made.

From industry's point of view, enrichment of products with antioxidants is only interesting when it is possible to inform the consumer by means of a claim. The use of claims should be based on sound and generally accepted science, the label should contain substantial information, it should be understandable to the consumer and legislation should be flexible enough to allow new product development. Claims might include wording such as the following: This product is high in, is a good source of, is rich in vitamin E (nutrient content claims). Vitamin E prevents the formation of free radicals, which negatively affect cell function (nutrient function claim). This product contains added vitamin E for a healthy diet (health claim). This product contains added vitamin E, which may reduce the risk of heart disease (medical claim, which is prohibited in all European countries). Obtaining scientific evidence for these different types of claims is progressively more difficult.

2. Dr D Müller (Procter & Gamble, Schwalbach am Taunus, D) gave a presentation entitled "Addition of Nutrients to Beverages: Examples of Industry Practice", with emphasis on experience in Germany.

Fortified beverages are common in Germany and Austria, less so in the United Kingdom and Belgium and are rarely available in Scandinavia and Southern Europe. In principle, any category of beverage can be fortified with antioxidants. Fruit-juice-based beverages have the longest tradition, but milk- and yoghurt-based beverages, sports and energy drinks, tea-based beverages, some soft drinks, and infant and small child formulations are commonly fortified with antioxidants. Nutrients that can be added to beverages include vitamins (vitamin C, the B vitamins, vitamin E, ß-carotene), minerals (calcium, iron, magnesium), trace elements, essential fatty acids, amino acids and fibre. Consumer acceptance is no problem in those countries with a tradition of fortification: not only is it accepted, it is expected. Vitamin C is the antioxidant most commonly used for the fortification of beverages, and consumers expect it to be present.

In Germany average vitamin C intake per capita is 100 mg / day, which translates into just under 3000 tonnes of ascorbic acid taken per year. The soft drink and fruit juice industries use more than 1000 tonnes of ascorbic acid per year, which is a significant contribution to intake. About 50% of vitamin C intake in Germany (50 mg / day) comes from refreshing beverages. Surprisingly, fruit juices account for only 16 mg / day. Thus, without fortification of refreshing beverages, vitamin C intake in some parts of the German population would be suboptimal if not marginal as judged by the German RDAs.

Certain questions should be asked before adding antioxidants to products: Is there a suboptimal intake in the target group? Will fortification lead to significant improvements in intake? Are there any adverse effects from the nutrient itself or because of its effects on the availability of other nutrients? Is the nutrient sufficiently bioavailable? Does the fortified product improve consumer choice? Is the fortification technically feasible? Will consumers understand and find the claims acceptable? Will the consumer like the fortified product? Fortification is only one tool for improving intakes. Improvement of nutrition information and education, optimisation of processing conditions and selection of plant cultivars rich in the desired antioxidant are even more important.

Thus, nutrient fortification of beverages is relatively common in those areas where it is permitted and can contribute very significantly to – but is only one of a number of strategies available for – improving nutrient intakes.

3. Dr P Lambelet (Nestlé Research Centre, Lausanne, CH) gave a presentation entitled "Natural Antioxidants: Manufacture and Applications to Food", which concentrated on sources of natural antioxidants, new techniques for manufacturing plant extracts with antioxidant properties and applications of antioxidants in foods.

Plant extracts are the principal sources of natural antioxidants and include vegetable oils, fruits, spices (rosemary, sage), seeds (oats, soybean), leaves (tea, mustard) and husks (rice, cocoa). Active compounds include the tocopherols, carnosic acid and carnosol (rosemary) and ascorbic acid.

Although antioxidants are ubiquitous in nature, only a limited number of raw materials such as vegetable oils and fats and rosemary leaves are used for manufacturing extracts with antioxidant activity. Methods of preparation include solvent extraction, mechanical procedures, molecular distillation, heating in oil at high temperature and supercritical fluid extraction. In the case of rosemary, solvent extraction with ethanol is followed by the addition of medium-chain triglycerides to obtain a liquid plant extract and then extraction with hexane. Mechanical extraction involves the addition of water and the use of a screw press or piston press. The advantages of mechanical over solvent extraction include the absence of organic solvent, lipophilic and hydrophilic extracts can be prepared, and antioxidants can be directly incorporated into oil, which protects them. In the case of rosemary, higher yields of antioxidant are obtained with mechanical extraction.

Basic research is needed to inform applications of antioxidants in food. Electronic spin resonance (ESR) spectroscopy can be used to follow the reaction of carnosic acid, one of the active compounds in rosemary, with methyl oleate at different temperatures. Rosemary extracts have good antioxidant activity when oriental noodles are fried in palm oil at 130°C but not as good as tertiary butylhydroquinone (TBHQ). Rosemary extracts have good antioxidant activity in animal fats but no effect in marine or vegetable oils and good antioxidant activity in emulsions compared with bulk oils. ESR studies of a "ternary mix" of vitamin E, vitamin C and phospholipid showed not only that vitamin C can regenerate vitamin E but also that phospholipid is involved in free radical generation. The ternary mix is not effective in milk products but is effective in ham, chocolate drinks and hazelnuts.

In summary, despite the fact that antioxidants are ubiquitous, industrial sources are limited, mechanical sources are effective means of extracting antioxidants from natural sources and the suitability of an antioxidant for a particular application is difficult to predict.

Ir K de Winter (European Consumers Organization, Brussels, B) gave a presentation entitled "Fortification of Food Products with Antioxidants: Consumers' Views".

A few years ago it seemed both clear and reasonable to say that increased intakes of antioxidants might confer protection against chronic diseases (such as cancer) by reducing free radical-mediated tissue damage. Now, because of the ATBC and CARET intervention studies, the issue has become more complicated. The results of these studies emphasize the importance of well-controlled intervention studies as the basis for recommendations to consumers.

Until recently, the addition of vitamins and micronutrients to foodstuffs in a number of countries was aimed mainly at the prevention of deficiency diseases, and this policy has proved extremely effective in Western countries. This policy should be continued as a means of maintaining good health. In this respect, it is important to find carriers of micronutrients which reach the entire population.

Some consumer organisations consider the addition of micronutrients to foodstuffs which do not naturally contain these micronutrients to be undesirable. It has become clear that various nutritive and non nutritive substances play a role in the antioxidant defence systems of the body. The actions of these substances are interrelated and not fully understood. Intervention at a single point in this complex system is likely to have unpredictable effects, particularly at pharmacologic doses. Some micronutrients are toxic at high levels. Consumer organisations particularly demand that attention be given to the fact that fortified products are no substitute for a healthy diet.

If the content of information messages to consumers changes frequently, consumers will lose confidence and the providers of those messages will lose credibility. Some consumer organisations urge caution with information messages, especially where evidence of efficacy is not convincing, as is the case concerning the beneficial effects of the addition of micronutrients. This cautious policy has certainly contributed to the trustworthiness of consumer organisations.

A large amount of data confirms the benefits for health of a balanced diet containing ample amounts of vegetables, fruits and cereals. At the same time, some alarming trends in the consumption of fruits and vegetables can be observed. In the Netherlands consumption has dropped 5% to 10% in the last 4 to 5 years, particularly in people less than 40 years old. Similar trends are apparent in the United Kingdom. The lack of convenience of fruits and vegetables, the increased availability of prepared meals which contain few vegetables, the few commercials on fruit and vegetables, the use of snacks other than fruits and the increasing lack of knowledge on preparing vegetables may play a role. Nutritionists and policy makers should pay greater attention to this decrease. With regard to health claims, consumer and other organisations believe that if they are made at all, they should be based on a firm body of scientific evidence and reflect views which are widely shared by the scientific community.

Session 3: Regulatory Framework

Dr B Mathioudakis (European Commission (EC) Directorate General III, Brussels, B) gave a presentation entitled "Regulatory Developments on the Addition of Nutrients to Foods Throughout Europe" in which he reviewed current legislative issues, described the activities of the European Commission in this area and explored the issues that will need to be addressed before European legislation can be harmonised on the addition of vitamins, minerals and trace elements to foods.

Five years ago the EC began to discuss the addition of nutrients to foods, and a discussion paper was issued in December 1991. Discussions with member states and other interested parties suggested that the great majority were in favour of harmonisation of legislation. However, a European Council meeting in Edinburgh in 1992 led to the decision to cut down on unneccessary legislation, and plans for harmonisation in this area were shelved. It was hoped that the application of the principle of mutual recognition would solve most problems, but in practice it was not applied. Renewed interest in the potential health benefits of micronutrients rekindled interest in harmonising legislation on the addition to foodstuffs of vitamins, minerals and trace elements. A scientific cooperation task force was set up whose objective was to establish the scientific basis for the development of measures for the protection of public health with respect to the addition of vitamins, minerals and trace elements to foodstuffs. A report whose aim is to provide objective data and information, but not to make recommendations, is being drafted.

At present, the limited addition of some nutrients is permitted in all member states and in some is compulsory to remedy or prevent specific demonstrated deficiencies (e.g., vitamin A and D in margarine, iodine in salt). Some member states prohibit the addition of minerals and vitamins in the absence of a demonstrated nutritional need. Others authorize addition on a case-by-case basis without clearly stated guidelines or regulations. Some allow addition to ordinary foods but impose limits for some or all nutrients. Others allow addition in general provided that the fortified food will not be injurious to health. For example, Austria, Luxembourg, the United Kingdom and to some extent Germany have a relatively permissive attitude. By contrast, there are limits for some nutrients but not for foods in Belgium and Greece. Thus, harmonisation will require consideration not only of technical and scientific issues but also of differences of ideology, policy, administrative attitudes and procedures. The primary issue to be resolved will be the scientific criteria by which the addition of vitamins and minerals to foods will be determined. The big questions will be nutritional need or safety.

Nutritional need as the sole criterion for the addition of vitamins and minerals to food permits their addition solely to prevent or remedy demonstrated nutritional deficiencies. Voluntary addition is not allowed because it is considered unnecessary (a well-balanced diet should provide all nutrients), it may confuse the consumer (it may invest certain foods with artificial nutritional properties), may lead to modification of dietary patterns (changes in food choice) and because foods with unnecessarily added vitamins and minerals are expensive – despite the fact that the consumer would have the necessary information for making his or her own choices. How can a nutritional need be defined? Food consumption data from different countries suggest that certain population groups have deficiencies in some vitamins, minerals and trace elements. Studies also suggest new beneficial effects of certain antioxidants.

Safety as the main criterion allows freedom to food manufacturers to add voluntarily vitamins and minerals to foods, new scientific findings to be explored by manufacturers, and consumers to exercise their power of choice and to achieve nutritional adequacy despite less-balanced diets that may result from changing socioeconomic factors and lifestyles.

Other factors influence the debate. Should there be any restriction on the addition of vitamins and minerals to foods, and if so should there be a positive or a negative list? If there is no problem of safety, why restrict their addition? Should the addition of minerals and vitamins be allowed to all foods or only to foods that do not naturally contain such nutrients, which might confuse the consumer and carry the risks of overexposure and undesirable interactions with other nutrients? The level of addition also causes concern. Setting maximum levels of addition in legislation might reassure the public and prevent abuse for promotional purposes. Maximum levels could be confined to those nutrients for which excess consumption has been demonstrated to lead to undesirable effects. Other issues include purity criteria of individual antioxidants, their bioavailability, and minimum levels and how these levels should be expressed. No official proposals for specific rules on claims have been put forward, but the idea has not been abandoned.

Following receipt of the report of the scientific cooperation task force, a discussion paper will be drafted on the addition of vitamins, minerals and trace elements to foodstuffs and to food supplements containing these same nutrients. It will not cover herbal products and other diet integrators or food supplements. Comments will be invited and the European Commission Services will then prepare appropriate proposals. The intention is to have binding measures, since member states asked for harmonisation of legislation. The proposals should be available by early 1997. Harmonisation will not be a simple operation of deciding technical issues based purely on science. Difficulties will arise over differences in attitude, ideology, policy, administrative procedures and perhaps fear of abuse of greater liberty given to manufacturers.

Perspectives from four countries

1. Dr R Harding (Ministry of Agriculture, Fisheries and Food, London, UK) reviewed the legislative position on fortification in the United Kingdom, the guidance available to manufacturers on the maximum levels of antioxidants to add, labelling and claims, and the contribution of the MAFF research programme on antioxidants.

The single criterion for the control of fortification in the United Kingdom is that food as sold should be safe. The primary legislation is the Food Safety Act (1990), which states that food should not be injurious to health. The act imposes a legal duty on manufacturers to ensure that their products are safe. The principles of due diligence apply, which means that manufacturers must carry out all reasonable safety checks and should have in place rigorous procedures for doing this. In practice, manufacturers take this responsibility very seriously. In the United Kingdom fortification of flour and margarine is compulsory. Voluntary fortification is permitted subject to the general controls in the Food Safety Act.

In the United Kingdom limited guidance is available to manufacturers on the maximum levels of antioxidants that can be added. The COMA report on Dietary Reference Values (1991) focused on sufficiency of intake, but where there was evidence of undesirable intakes, e.g., retinol, this was indicated. However, a comparison of the recommendations in the COMA report with those of the EC Scientific Committee on Food (SCF) reveals that there is little consensus on undesirable levels of micronutrients. The report of a working group of officials (the Denner report) on dietary supplements and health foods (1991) proposed that any maximum level should be related to undesirable levels rather than reference nutrient intakes, which has no logical connection with potential harm. Data from the National Diet and Nutrition Survey (1986) show that with the exception of retinol, undesirable levels of micronutrients do not result from food alone. As a result the U.K. Chief Medical Officer (CMO) advises pregnant women not to consume liver or supplements of vitamin A.

All prepacked foods must comply with the requirements of the EU directives on labelling. No claim can be made about a micronutrient unless it appears on a list and is present in a significant amount. A significant amount means, as a rule, 15% of the RDA, which is supplied in 100 g or 100 mL food or a portion. The words “as a rule” provide flexibility or uncertainty because when foods provide a nutritionally significant amount of a vitamin or mineral, this can be declared even if it is less than 15% of the RDA. In addition, in the United Kingdom, if manufacturers wish to say a food is rich in or an excellent source of a nutrient, 50% of the daily allowance must be present in 100 g or 100 mL food or a portion of the food; for other claims a sixth of the daily allowance must be present.

Labelling legislation prohibits medicinal claims (treatment, cure or prevention of disease) for foods, but the possibility of making nonmedicinal health claims has led to the development of functional foods. Consumers have expressed concern over the value of such foods in a diet and the validity and accuracy of the claims, and the food industry is anxious to have clear rules about how such foods can be described. In 1990 the Food Advisory Committee (FAC) recommended that health claims should be printed only if justified in relation to recommendations made by the CMO and must relate to the food as eaten, labelling must show consumers that the claim is justified, the label should give a full description of the food, the role of the food in the whole diet should be

explained, health endorsement schemes to promote types of food should be banned and health endorsements made by individuals should be banned. However, the FAC is currently reexamining this area.

The views of the CMO on antioxidants are set out in the COMA report on cardiovascular disease (1994), which states that "the evidence for a protective effect of the antioxidant vitamins C and E is persuasive but not yet conclusive. Other substances in food might be important. Until the results of a number of randomised intervention trials currently underway are known, public policy recommendations recommending increased intakes of specific antioxidant nutrients would be premature. We recommend a diet rich in vegetables and fruit containing nuts and seeds and with less saturated oils partly substituting for more saturated fats which increase intake of these nutrients and is conducive to general health. The potential risks of purified supplements in pharmaceutical form are not known. Recent evidence suggests it would be unwise to assume that they are safe. They are not recommended as a widespread public health policy for coronary heart disease prevention".

MAFF funds a major programme of research in this area under the management of Professor A. Diplock. Defining the optimal intakes of antioxidant nutrients is a major objective of this programme. Areas of interest include the dose-response relationship between intakes and cellular function, studies of absorption, transport, cellular uptake and metabolism of antioxidants, and noninvasive methods to evaluate free-radical-mediated tissue damage (biomarkers). The programme consists of about 20 projects carried out in different centres around the United Kingdom and costs about £1.5 million a year. It is a model being examined by other funding agencies and will provide scientific data for consideration by future expert committees considering the role of antioxidants in human nutrition.

2. Professor A Bruce (National Food Administration, Uppsala, S) reviewed dietary recommendations, health claims and the rapidly evolving legislation on dietary supplements in Sweden.

In 1989 there was a national survey of food purchase and consumption in Sweden. One individual in each of 2000 households completed a 7-day record. Energy intakes were underreported by 20%, but it is not known whether the same is true for nutrients. For men and women, respectively, intakes of vitamin C were 71 and 75 mg, vitamin E 7.7 and 6.2 mg, ß-carotene 1.8 and 2.0 mg and selenium 36 and 28 µg. The recommendations of the Nordic countries emphasize the nutrients providing energy, particularly a decrease in fat intake and an increase in starch and dietary fibre, which if fulfilled will lead to recommendations on micronutrients being automatically met. The Swedish recommendations use a food circle divided into seven segments to achieve variety. Vegetables and fruits are in three groups: fruits and berries, pulses and legumes, and root vegetables (potatoes are occasionally separated from this group). Every day something should be selected from each segment. Dietary guidelines include moderate consumption of alcohol, variety and the recently added recommendation to consume fruits and vegetables two to three times a day. The plate model has been developed to emphasize the importance of the starchy components (40%) and vegetables (40%). Sweden has a liberal and, at the same time, a restrictive attitude toward food fortification. About 75% of iodine intake is from fortified salt, 50% of vitamin D intake is from low-fat milk or margarine, 30% of vitamin B-6 intake is from fortified cereal products but only 10% of ascorbic acid is provided by fortified products. Only a few foods for special dietary uses are fortified with vitamin E or selenium, and ß-carotene is used largely for colouring. Swedes are very reluctant to accept new fortified products.

Until recently, Sweden had a very liberal attitude toward vitamin and mineral products and accepted a number of claims not accepted in other countries. A committee was established by the Food Administration and Swedish Medical Products Agency to examine this area and has identified three groups of products. Food supplements which provide a significant fraction of recommended intakes, fulfill good manufacturing practice and no claims would be made available for sale without notification. Products where the doses are high (three times the recommendation) would be regarded as pharmaceutical preparations and would be sold through the pharmacist, although this does not mean that a doctor's prescription will be needed. Claims in relation to the legislation on drugs would be accepted. Products containing intermediate doses are the most problematic (e.g., ginseng), and manufacturers will have to apply for permission to make claims. Comments on these proposals have been invited and are being reviewed.

Sweden accepts health claims under certain conditions, but none are directly related to antioxidants. Claims are allowed for obesity, blood cholesterol, blood pressure, atherosclerosis and constipation but not for cancer. Claims are in two parts. A statement about the whole diet must be given first followed by information on how the product relates to the diet. In the case of obesity, for example, a statement that a diet with a low or reduced energy content is a significant factor in the prevention and treatment of obesity could be followed by an informative statement to the effect that this product has a low or decreased energy content.

3. Dr J-I Arranz Recio (Ministry of Health and Consumption, Madrid, E) discussed two Spanish legislation projects on enriched foods and on food supplements and food integrators.

Spanish people usually eat a Mediterranean diet consisting of plenty of fruits, vegetables, fish (especially blue fish) and olive oil. As a result, the addition of nutrients to foods for public health reasons is not a high priority in Spain. Although supplementation to prevent iodine deficiency disorders is still considered important, no clear evidence suggests that supplements of other nutrients such as antioxidants or fibre would improve health in Spain. However, undernourished population groups may still exist in Spain. The antioxidant properties of single nutrients or synergistic combinations may yet prove to reduce the risk of degenerative disease. It is also possible that some of these nutrients will not reach their optimal concentration when supplied by diet alone. It is still not clear that the protective properties of certain nutrients are truly independent of other life-style factors. The priority thus remains the protection of health by preventing the misuse of nutrient supplements rather than by encouraging their use.

The addition of nutrients to foods cannot be easily accommodated by current legal frameworks. So-called nutraceuticals try to gain access to the market as diet foods. However, they cannot be given this status because they do not fulfill the requirements of the dietetic Framework Directive 89/398/EEC, they do not comply with the labelling standards and they make medical claims, which are prohibited. In cases where product composition justifies a claim, the product is covered by the definition of drug in Directive 65/65/EEC. Nutraceuticals are half-way between a food and a drug, trying to benefit from the advantages of both while avoiding the controls on each. Delays in the harmonisation of legislation in the European Union have not help clarify which nutrients can be added.

Some member states, including Spain, have attempted to clarify the status of enriched foods, food supplements and food integrators within the food legal framework while avoiding the pharmaceutical legal framework. The Spanish approach is to decide which nutrients can be used, to establish the highest levels allowed and to make the legislation compatible with Nutritional Labelling Directive 90/496/EEC and the labelling and publicity messages compatible with the principles of Directive 79/112/EEC.

4. Dr W Glinsmann (Consultant to the Food and Drug Administration, Washington DC, USA) presented a comprehensive review of the use of antioxidants for health effects, functionality and the prevention of rancidity, fortification and functional foods in relation to safety standards and claims, the BHA controversy and the possible role of Codex in international harmonisation of legislation.

The U.S. Federal Food, Drug and Cosmetic (FD&C) Act (1938) classified substances as foods or drugs according to their function. Food and drugs were not viewed as a continuum. Drugs are substances used to diagnose, cure, mitigate, treat or prevent disease. Foods are substances used as food or drink (or substances used as components of food or drink) which provide taste, aroma, nutritive value and/or technical effect. For many years there was no disease- or health-related wording on the food label. Between 1938 and the late 1960s the legal view of food was that it was unrelated to disease. A White House conference on food, nutrition and health (1969) stressed the potential of labelling foods for health and the use of modern technology to produce more nutritious food. At the same time, a variety of factors combined to place dietary supplements in a category of their own. The 1976 Proxmire amendment describes what a product for special dietary use is and tells the Food and Drug Administration (FDA) that it must regulate vitamin or mineral supplements on the basis of safety only and not according to dose. Infant formulas used to treat inborn errors of metabolism are clearly drugs in the sense that they are used to treat and manage disease but were placed in the category of foods for special dietary use, referred to as medical foods. Thus, the distinction between foods and drugs began to break down. In the 1980s the Infant Formula Act was passed and the Orphan Drug Act defined medical foods as foods used under a physician's guidance for the management or treatment of disease, i.e., are druglike in their action. Infant formulas that were used to manage children with inborn errors of metabolism were redefined as "Exempt Infant Formula" because their composition was exempted from the requirements that apply to regular infant formula. In 1990 Congress gave the FDA the authority under the Nutrition Labelling and Education Act (NLEA) to allow health claims on food labels, and in 1994 the Dietary Supplement Health and Education Act redefined the term dietary supplement and provided for special labelling and statements of nutritional support.

Fortification policy was established in the 1970s to replace vitamins and minerals lost during food processing, and during the 1980s regulations became guidelines which dealt with standards of identity, foods that had common or usual names, nutrition quality guidelines and imitation status. At present, a variety of ingredients can be added to the food supply provided they have a reference daily intake (RDI) or daily reference value (DRV), with 10% added back considered a good source and 25% added back a very good source. Characterising descriptions on the food label require an approving regulation. In the future, dietary supplements may provide a more targeted approach than food fortification to deliver a nutrient to a target population e.g., folic acid.

There is no definition of a functional food, but it is a commonly used term to refer to many components of the food supply which have health effects. Functional components of food are substances which are considered food but not primarily for taste, aroma or nutritional value. They are not essential for growth, development or the maintenance of normal biological processes. They may or may not be nutrients but share the ability to modify the structure and function of the body in a manner which alters performance or risk of disease. They are considered to have effects either in the general population or in easily identified subpopulations, and they adhere to food

safety standards. They are not drugs, and food labelling and manufacturing practices apply. Antioxidants may be considered functional by virtue of having potential for such actions as anti cancer and anti cardiovascular-disease effects or being modifiers of oxidative damage and defence mechanisms. Other food components may be functional because they are anti mutagens and anti carcinogens, inducers of enzymes of xenobiotic metabolism, or inhibitors of enzymes which synthesize molecules involved in the spread of microbial infections and perhaps cancer. Other functional components act as probiotics, prebiotics, neuroregulatory substances, antihypertensives and a variety of immunomodulators.

In the United States there are no simple rules on food safety and on which safety standards apply. Something naturally present in food adulterates the food only if it is ordinarily injurious to health. If something is added accidentally during food processing, a somewhat higher standard applies. Antioxidants added for a functional effect or a migrating material from packaging must meet the highest 1958 food additives safety standard, which is reasonable certainty that they will cause no harm under their cumulative conditions or use. According to the Dietary Supplement Health and Education Act, a dietary supplement now has a lesser safety standard, i.e., it must present a significant or unreasonable risk of illness or injury before it is considered an adulterating compound. Benefit and risk considerations used for drug approval are not appropriate for the food supply. New additives for general foods and for foods for special dietary use require premarket determination and must be safe for their intended use (food additive approval or GRAS [generally recognized as safe] determination). Exempt infant formulas and medical foods are considered on a case-by-case basis. Medical foods are excluded from general nutrition labelling under the NLEA but must be safe for intended use and contain approved food additives and GRAS substances. Dietary supplements by definition do not fall under provisions of the food additives amendment to the FD&C Act and may be marketed without premarket approval, but FDA has the responsibility for looking at them post market. Hence, they are the least controlled category in terms of safety requirements.

The NLEA requires the declaration of specified nutrients, the quantity per serving and the percentage of a daily value per serving. It allows authorised content claims, quantitative descriptors, authorised comparative claims and health claims. Health claims must be authorised by regulation, describe the relationship between a food substance and a disease, be described within the context of the total diet and meet the standard that there is significant scientific agreement among qualified experts. The Dietary Supplement Health and Education Act (1994) allows for statements of nutritional support, also called structure-function claims. Statements may deal with the claim of a benefit related to a classical nutrient deficiency disease and disclose the prevalence of the disease, or may describe the role of a dietary ingredient intended to affect the structure and function of the body. A statement characterises a documented mechanism by which a dietary ingredient acts to maintain such structure and function, it must be truthful and not misleading, the manufacturer is responsible for substantiation and must notify the FDA. The manufacturer also must add to the label that this statement has not been evaluated by the FDA and that this product is not intended to diagnose, treat, cure or prevent disease.

A dietary supplement has a very precise description. It is a tablet, capsule, liquid, powder or soft gel; it cannot be represented as a conventional food, sole item of diet or total diet; and it must be labelled as a dietary supplement. It can contain vitamins, minerals, herbs, botanicals other than tobacco, amino acids, concentrates, metabolites, extracts or even articles previously approved as drugs, antibiotics or biologicals provided they were first marketed as dietary supplements. Their contents must be declared and the part of the botanical dietary ingredients present stated. Third-party literature may now be placed in the same location as the dietary supplement, but must not be misleading and must be physically separate from the supplement. Stickers on supplement products similar to drug packaging to sell the product are not allowed.

Butylated hydroxyanisole (BHA) is one of the long-standing antioxidants used to prevent rancidity in oils. Letters in the 1940s and 1950s provided the basis for prior sanctioning and for placing BHA on the GRAS list without a formal review of the science. Several food additive regulations, even after the passage of the 1958 food additives amendment, continued to allow BHA to be used for food preservation. In the 1980s it became clear that at very high levels, BHA was a tumour-producing substance in the forestomachs of a variety of rodents. In 1990 the FDA was requested to revoke the GRAS petition and to list BHA among substances which are prohibited for use in food. After requesting comments, the FDA felt that an expert outside panel was needed to review the data. The Federation of the American Societies of Experimental Biology (FASEB) invited the submission of all types of relevant scientific information in an open hearing on the safety of BHA. The final report (1994) found that BHA was not a class I primary carcinogen. There was a threshold effect, but at current levels of exposure this was not reached and hence there was no risk of cancer in humans. However, BHA may be a category II or III carcinogen. Proliferative effects at high concentrations when BHA acts as a prooxidant could not be ruled out. The Delaney clause in the food additive amendments states that if anything causes cancer in animals or humans it cannot be approved as a food additive. Should this clause remain in effect, many components will have to be removed from the food supply even though they have a threshold effect and the science exists to demonstrate no harm. The implications of the Delaney clause are currently being examined by the US Congress. The clause has been deleted recently with regard to certain pesticide residues.

Member governments of the World Trade Organization have agreed to use relevant international standards such as Codex except when they consider that, based on scientific evidence, these standards will not adequately protect public health. It would be wise to submit the science on antioxidants to Codex. Assessment of risks must be transparent. The FDA belongs to several of these committees (food labelling, food additives, food hygiene, nutrition and food for special dietary uses). Nutrient content claims and health claims are under discussion in Codex. For nutrient content claims the question is where to draw the line and whether health claims are advisable in the international arena. The key points for dietary supplements are whether there should be any limitation on the amount of ingredients and whether claims should be allowed. Harmonisation will require discussion of these issues in an international arena such as Codex.

Session 4: Panel Discussion

1. Scientific overview on antioxidants

Protective factors in foods: There are numerous protective factors in foods, many of which are not antioxidants, e.g., the anticarcinogenic properties of isothiocyanates in cruciferous vegetables. Isolating each one and determining its safety and efficacy not only is impractical and expensive but also may lead to loss of protective activity if this depends on the food matrix and synergy between the protective factors. The study of groups of substances with respect to efficacy and safety may be a more practical approach.

Total antioxidant activity: The Free Radical Research Group has developed methods at Guy's Hospital and St Thomas Hospital, London, to determine the total antioxidant activity of beverages such as fruit juices by measuring their ability to quench the activity of a free radical. The total antioxidant activity of beverages almost always exceeds that of the sum of the contributions of the known antioxidants.

Antioxidant status: There is no general agreement on a good measure of antioxidant status. What is needed is a measurable common factor through which all antioxidants work. Plasma vitamin E is maintained not only by dietary vitamin E but also by other antioxidants such as vitamin C and polyphenols, which spare it. Plasma vitamin E does not reflect tissue vitamin E. Adipose tissue vitamin E is a better indicator of long-term intake. At the cellular level, glutathione status may be a good measure of antioxidant status.

Oxidative damage: There is a need for the refinement of methods (biomarkers) for measuring free-radical-mediated damage to nucleic acids, proteins and polyunsaturated fatty acids in humans *in vivo* suitable for use in studies of nutrient need and safety. This is one objective of the MAFF antioxidant research programme.

Bioavailability: There is very little information on antioxidant bioavailability *in vivo* in humans, and this should be a major target of future research. Bioavailability is the sum of absorption from the gut, transport in the blood, cellular uptake and metabolism. These processes are ill-defined for many antioxidants. It is not known whether the bioavailability of an antioxidant from a supplement is the same as that from a food matrix. This would have important implications for the practice of restoration. Although processing may decrease the antioxidant content of a food, it may simultaneously increase its bioavailability.

2. Potential for product improvement

Safety: Antioxidants can have prooxidant effects at high concentrations, although such high concentrations may never be achieved in human tissues *in vivo*. Quercetin is mutagenic in bacterial test systems. In intervention trials the possibility of harm from ß-carotene in heavy smokers has been suggested. In the United Kingdom, pregnant women are advised not to consume liver or supplements of vitamin A, although the rationale for this is subject to question. Biomarkers which are predictors of long-term health gain are needed to assess safety. There is no evidence that fortified foods have detrimental effects.

The addition of antioxidants to foods: Consumers understand the need to restore nutrient levels to those originally present before processing. EU member states differ enormously in their fortification policies. However, experience in Germany has shown that fortification of beverages with vitamin C can and does make a significant contribution to intake. Consumers find acceptable the fortification of foods with antioxidants they normally contain, e.g., vitamin C to fruit juices, vitamin E to oils.

Optimising antioxidant content: Everyone involved in transforming and transporting food from the field to the plate has a role to play. The food industry has a responsibility to optimise processing, storage and transport conditions to maintain the antioxidant content of foods. Plant breeding, harvesting practices and raw material selection to date have had very little impact on optimising the antioxidant content of foods and should be given priority in the future. The consumer can make a contribution by adopting good cooking practices and using appropriate storage and transport conditions.

Fruits and vegetables: It is desirable to increase fruit and vegetable consumption because it remains the best way of delivering the totality of protective factors to the consumer. However, there are barriers to achieving this. Tradition, lack of and / or confused knowledge, availability, quality, cost and convenience are all factors. By contrast, Mediterranean populations maintain a high level of fruit and vegetable intake. The way forward is probably through nutrition education of the young. However, as long as people remain reluctant to increase their fruit and vegetable intake, there will be a role for the addition of antioxidants to food.

3. Regulatory framework

Population subgroups: Dietary advice tends to be aimed at the population as a whole rather than at subgroups. This may change in the future as the techniques of molecular biology identify more prevalent genotypes with different susceptibilities to nutrients. In the United States there are orphan products and foods for special dietary uses aimed at special populations which are covered by specific legislation but which do not affect the food supply of the majority of the population.

The relevance of RDAs to antioxidants: RDAs are based on classical nutritional deficiency diseases rather than on their ability to prevent chronic disease. However, it will be difficult to set standards without RDAs or something very similar. The key question for the regulatory framework is whether the measures will be based on nutritional need or safety.

Harmonisation of legislation: Despite the desire for harmonisation of legislation by EU member states, this remains a distant prospect although a timetable is in place. Even if all of the science on nutritional need and safety were in place, there would still be difficulties over differences in attitude, ideology, policy, administrative procedures and fear of abuse of greater liberty given to manufacturers.

Foods versus drugs: The distinction between foods and drugs is becoming less clear in the United States.

Enforceable definition of claims: Claims present problems, and definitions are needed to aid the process of substantiation, e.g., nutrient content claims, nutrient function claims, health claims and medical claims. Success will depend largely on the harmonisation of legislation.

Acknowledgement

ILSI Europe would like to thank Dr J.C. Stanley for acting as the rapporteur of the workshop and for writing this report.

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ISBN 1-57881-016-7