

## Summary Report

# Functional Foods: Scientific and Global Perspectives

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### Key symposium messages

#### *Session I. Global View on Functional Foods*

The symposium opened with a review of the functional food concepts in place in various regions around the world. This global overview included Asia, Europe, Latin America and North America. The session touched on differences in culture and beliefs with respect to foods, functional foods and medicines, and their impact on health and disease.

In Asia, where functional foods have been regarded as an integral part of the culture for many years, there is a firm belief that foods and medicine come from the same source and serve the same purpose. However, scientists and regulators have only recently begun to agree that the functionality of functional foods should be found in whole foods rather than in their individual components. In Japan, research on functional foods started in the early 1980s. In 1991, a specific regulatory framework concerning Food for Specific Health Use (called FOSHU) was introduced, which made it possible to make limited health claims after receiving approval from the Ministry of Health. The key to success for food manufacturers is to develop products that are accepted by consumers and are consistent with the consumer's understanding and appreciation of functional foods within the existing culture. Because the state of a person's health may range from optimal to a state of disease, it is believed that functional foods have a major role to play in all states of health, including maintaining health and preventing disease.

In contrast to Asia, the concept of functional foods in Europe is relatively new, and at present there are no Europe-wide regulations in place. In developing health claims legislation, the EU has adopted a working definition resulting from a European consensus published in 1999: 'a food can be regarded as functional if it is satisfactorily demonstrated to beneficially affect one or more target functions in the body, beyond adequate nutritional effects, in a way which is relevant to either an improved state of health and well-being, or reduction of risk of disease'.

The target of functional foods is seen as clearly different from that of drugs, which are aimed at preventing or curing diseases.

The scientific underpinning of health claims may derive from experimental studies and/or epidemiological and intervention studies where the use of biomarkers is regarded as a key element. The EU PASSCLAIM project (Process for the Assessment of Scientific Support for Claims on Foods) is intended to provide industry, academics, consumer groups and regulators with the means to evaluate the scientific basis for health claims. Although there is increasing demand by the European consumer for healthier food products, so far few functional food products have actually reached the market place. This is due partly to the fact that developing adequate scientific support for health claims can be relatively expensive and time-consuming. Moreover, some food manufacturers struggle with how best to communicate diet- and health-related information to consumers.

Research on food and nutrition has been an important topic in the EU Framework Programmes for Research and Technology Development of the European Commission. In the 1990s a significant number of EU projects addressed issues such as fibres and pro- and prebiotics, whereas more recent EU programmes focus on areas such as antioxidants, vitamins and phyto-oestrogens, as well as the socio-economic aspects of nutrition and health.

Although there is no specific definition of functional foods in Latin America, the concept of functional foods is presently under discussion in several Latin American countries. Brazil is in the process of developing health claims, and although Argentina does not have health claims regulations in place, it does approve claims on a case-by-case basis. Provided there is adequate scientific validation, both countries have approved nutrient function and disease risk reduction claims for specific food products. Usually, locally conducted research to support product efficacy for health claims approval is requested.

The Latin American population suffers from diseases of nutrient excess as well as nutrient deficiency. Micronutrient

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**Abbreviations:** COX-2, cyclo-oxygenase-2; CVD, cardiovascular disease; FOSHU, food for specific health use; GI, gastrointestinal; ILSI, International Life Sciences Institute; NOAEL, no observed adverse effect level; PASSCLAIM, Process for the Assessment of Scientific Support for Claims on Foods; SYNCAN, Synbiotics and Cancer Prevention in Humans.

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deficiencies exist for I, Fe and vitamin A, and sub-optimal intakes of Zn, folate, Ca and Se are reported. Nutritional excess includes energy, fats, carbohydrates, cholesterol, salt and sugar, in addition to decreased physical activity. There is thus a need in Latin America for functional foods that contain specific micronutrients through fortification, processing and genetic engineering. Although most consumers in the region are not aware of functional foods, they are concerned with their diet and health. In this respect, 'natural foods' are perceived as healthier than processed foods. Although the consumer associates food with healing and curing diseases, there is a clear distinction between the roles of foods and drugs.

It was stressed that basic nutrition research on the health impact of locally produced products such as grains and fruits in Latin America is inadequate. Epidemiological and clinical research is needed to correlate regional foods/diets and diseases. Also needed is a better understanding of the genetic background of the populations and what influence this may have on health and disease states.

In the United States and Canada there is also no universally accepted definition of functional foods, but 60% of the people select foods they believe are functional. The present understanding of the US population appears to be that functional foods include both nutrients and non-nutrients. Foods and drugs are clearly distinguished by their intended use and presentation, as well as by their targeted population. In the United States, functional attributes can be communicated through health claims, structure–function claims, and nutrient content claims. The Food and Drug Administration must approve health claims, and fifteen claims have been approved to date. These claims describe the relationship between a food component and a disease or health-related condition. The approval of claims has been based on an extensive review of existing scientific literature, in the form of an authoritative statement of a scientific body of the US government or the National Academy of Sciences. Nutrient content and structure–function claims are clearly defined in the regulations and do not need to be approved by the Food and Drug Administration. Canada also has undertaken initiatives to establish nutrient and health claims regulations similar to those in the United States.

Although both scientists and regulators are gaining more experience and scientific understanding of health and nutrition, the complexity of the issues continues to grow. Recognising the role of food consumption patterns in growth, development and disease risk is important to understanding how diet influences these areas. There is a myriad of possible interactions between specific dietary components and specific genetic pathways involved in health. Understanding these interactions will provide guidance in establishing dietary recommendations and communicating benefits to targeted populations.

*Session II. Scientific Basis of Biomarkers and Benefits of Functional Foods: Enhancement of Function and Reduction of Disease Risk*

The second session reviewed the scientific support currently available for biomarkers that indicate enhancement

of physiological function and disease risk reduction. Regarding enhancement of physiological function, the session included gastrointestinal (GI) physiology, the immune system, physical performance, and behavioural and psychological functions. Regarding disease risk reduction, the session focused on biomarkers for evaluating the effects of functional foods on the risk of cardiovascular disease (CVD), obesity/diabetes, cancer and osteoporosis, all elucidated with examples. The need for well-designed placebo-controlled studies in target populations was discussed, as were the identification and validation of appropriate surrogate biomarkers. Session highlights follow.

GI tract physiology and functions are related to meal-induced responses and longer-term adaptive changes, to the mechanisms of nutrient absorption and digestion, and to the impact on metabolic effects in other organs. The digestion and absorption of food are regulated by several factors such as the hormone cholecystokinin, which is released in response to a meal, thereby preparing the GI tract to digest food and ensuring a steady rate of nutrient absorption. Cholecystokinin also signals short-term satiety and can be regarded as a mediator of satiety and feelings of hunger. A second example focused on the digestion and absorption of carbohydrates and their impact on glucose, insulin and energy metabolism. The role of non-digestible fermentable carbohydrates for GI function, including the microflora of the large intestine, and potential systemic consequences (e.g. on the immune system) highlighted the importance of this organ system. Also addressed was the role of viscosity in relation to the metabolic effects of soluble dietary fibres on nutrient absorption rate, plasma cholesterol and glycaemic response. Research was called for to elucidate the bioavailability of bioactive compounds, the role of the food matrix, and health-related outcomes originating from modulation of the gut microflora.

The functioning of the immune system and its role in protecting the host were reviewed, as were factors such as the balance between pro- and anti-inflammatory effects, inter-individual variations and available biomarkers. Although it is clear that individuals with sub-optimal immune responses are more susceptible to infectious agents, it is not clear how modulation of the immune function in healthy individuals relates to susceptibility to infections. Food components can play a key role in maintaining optimal immune function; undernutrition appears to impair this function and, consequently, susceptibility to infections. Animal and human studies have demonstrated that optimising food intake through nutrient fortification can restore resistance to infections but that excesses of particular nutrients can lead to impaired immune function. Moreover, specific dietary components can increase a particular immunological parameter while decreasing another. Among the most studied nutrients in this regard are vitamin A, vitamin E and Zn. There is emerging evidence that probiotic bacteria may improve host immune function, although, at present, human data are still controversial and the relevance of such immune modulations for human health is unclear. To correlate dietary intervention, immune function and consequent health

impact, research should also focus on whole-body parameters, such as the incidence of infections, in addition to individual immune parameters.

During the last century there were significant changes in elucidating the role of diet in exercise and physical performance. It was shown that exercise-induced reductions in muscle glycogen correlate well with the development of fatigue and that the intake of carbohydrates (versus protein or fat) improves performance. Nutrition research to identify nutrients that support energy metabolism, promote fluid balance, increase muscle mass and improve overall performance (e.g. caffeine, creatine, ribose, certain amino acids and L-carnitine) led to the development of tailored foods and drinks that are easily digestible, help sustain the exercise load and improve the recovery of athletes from intense exercise. So far it is recognised that sports nutrition research is, in scientific terms, the best-established functional food area. Accordingly, measurement techniques (for gastric emptying, rate of intestinal absorption, appearance of substrates in blood and subsequent storage) and laboratory exercise protocols that measure performance accurately have been developed and validated. As in other functional food areas, solid scientific underpinning of product claims is a prerequisite.

Interest in functional foods for the enhancement of behavioural and psychological functions is targeted to foods that can influence appetite and satiety, vitality, stress and other subjective states of mood and well-being, cognitive and mental performance, and sleep. In principle, biological markers for behavioural and psychological responses could be identified, but the complexity of these responses would make their identification far from simple. Because of progress in, for example, the field of appetite and satiety control via specific GI and metabolic responses, and in mood research via changes in plasma profiles of metabolites, these areas would present good opportunities for further research. Food intake and hunger rating profiles are often used as biomarkers for appetite and satiety. In this respect, it has been shown that proteins increase satiety more than carbohydrates and fats. There also is a clear need to distinguish between short-term postprandial responses to food ingestion and long-term effects of dietary adjustment, because they require different research methodologies. Research related to cognitive performance needs psychobiological assays. Several types of trials have measured different abilities, but no unambiguous general biomarkers are available. It is necessary to ensure that foods that provide improvements for one phenomenon do not exert deleterious effects on other bodily functions. On balance, there is no clear conceptual framework to develop and assess the efficacy of foods to improve behavioural and psychological functions, and there is a need for markers that represent real-world situations.

There appear to be many potential biomarkers for chronic diseases such as CVD, diabetes, cancer and osteoporosis, but both their ease of use and level of validation may vary significantly. It was proposed that four critical features should characterise effective biomarkers for disease risk: appropriate response in clinical or dietary trials, consistency with epidemiology, appropriate response

in hereditary disease states, and plausibility of mechanism. When these criteria are applied to the plethora of biomarkers that have been proposed for CVD, only blood pressure and blood cholesterol levels stand out as valid markers. However, arterial intima-media thickness also appears to be an appropriate non-invasive marker for CVD with important potential use in dietary interventions, e.g. its positive association with blood homocysteine levels. Various indicators of endothelial function have been identified (e.g. vascular cell adhesion molecule 1, intercellular adhesion molecule 1 and *p*-selectin), but there is little evidence that changing these indicators will affect the disease risk. Markers are also available for CVD other than atherosclerosis, and in this context the measurement of thrombotic components, inflammatory markers and arrhythmia were highlighted.

There is an urgent need for efficacious functional foods for the control of obesity in view of the scope of the obesity epidemic, which is paralleled by a corresponding growth in type 2 diabetes. There are various non-invasive markers of obesity (e.g. BMI, dual-energy X-ray absorptiometry scanning, bioelectrical impedance, and computerised tomography and magnetic resonance imaging scanning for visceral obesity). Fat replacers, fat-binding agents and ingredients that increase energy expenditure provide clear opportunities for developing functional foods in this area. It has been suggested that specific fatty acids such as medium-chain fatty acids may have a role in weight reduction. However, there is no conclusive evidence of their efficacy, and GI implications may limit their incorporation into diets at higher levels. Results at the cellular level indicate that high Ca concentrations may increase fat oxidation, but as yet there are few supportive *in vivo* data. A potential promising area may be functional foods that increase satiety. Foods also can be used to reduce the risk of diabetes, and a variety of biomarkers can be applied for their evaluation (e.g. oral glucose tolerance tests, fasting blood glucose, insulin levels and insulin sensitivity). At present, however, there are few well-executed nutritional studies in this field.

In the area of bone health and osteoporosis, many of the valid biomarkers, e.g. fracture frequency and bone mineral content/density, require long-term intervention. Although bone mineral content measurements, for example, are relatively simple and non-invasive, two to four years of intervention are needed to provide meaningful data. Shorter-term markers are based on the measurement of Ca metabolism/excretion or on urinary markers of bone formation and resorption. A new technique based on <sup>41</sup>Ca tracer technology appears to provide a highly sensitive and direct measure of calcium release/bone loss and requires relatively small numbers of subjects to achieve statistical power. Opportunities for developing functional foods in this area include in particular those that enhance Ca resorption, such as casein phosphopeptides, whey protein concentrates and non-digestible oligosaccharides.

In the field of cancer risk a number of potential biomarkers have been identified, especially for colorectal cancer, including mucosal markers (e.g. cyclo-oxygenase-2 (COX-2), DNA repair capacity, microsatellites), faecal markers (e.g. calprotectin, AP-1 activation, cytotoxicity,

genotoxicity) and immunological/inflammatory markers (e.g. natural killer cells, COX-2 suppression). Many dietary intervention studies on prevention of colorectal cancer have been carried out on adenoma patients with polyp recurrence as the endpoint, but the relevance of such biomarkers for the general population is not yet established. For most of the markers of colorectal cancer in use, there is clearly a need for further and more systematic evaluation. These markers are currently being applied in a major EU-funded intervention trial (Synbiotics and Cancer Prevention in Humans, SYNCAN), and this study is expected to provide valuable information on their utility and suitability. Given the epidemiological associations of dietary components and cancer risk, there are good opportunities for developing functional foods in this area, particularly from plant sources.

Genomic and post-genomic technologies were highlighted as having great potential for the identification of new biomarkers for disease risk and for intervention trials, with proteomics being potentially most valuable. However, there was general consensus that the scientific community needs to arrive at well-validated biomarkers. If these are not available, it may be more appropriate to invest in a small number of well-conducted trials with clear disease endpoints or other 'hard' markers than in a larger number of shorter-term studies based on poorly validated biomarkers.

A warning note was sounded that dietary regimens that reduce the risk of one disease may increase the risk for another, e.g. an increased Ca intake may reduce the risk for osteoporosis but also may increase the risk for prostate cancer.

Table 1 lists the biomarkers for well-being and disease risk reduction discussed at the meeting.

### *Session III. Human Genetic Variability and Safety of Functional Foods*

Emerging information about genetic variation and its impact on human health makes this an exciting new area related to understanding the effects of functional foods. Single nucleotide polymorphisms occur frequently, but there is little evidence that such variation in genetic expression explains a significant portion of the variability seen in the response to disease risk factors, especially those linked to dietary components. Nevertheless, the emerging information on the impact of genetic variability signals a significant potential for research. The difficulty

of showing actual health effects from nutrients was acknowledged. For example, a recent trial with vitamin E and a multimicronutrient supplement in elderly individuals did not show any improvement in infection rates. In addition, elevated homocysteine levels are associated with increased risk for CVD, but evidence of direct causality is lacking. Variation in the gene coding for methylenetetrahydrofolate reductase, a folate-dependent enzyme responsible for remethylation of homocysteine to methionine, has been examined as a way of addressing the causality issue. The majority of epidemiological studies examining individuals with this mutation and the resulting elevation in homocysteine, however, did not find an association with CVD risk. Nevertheless, evidence is emerging that elevated homocysteine levels are positively associated with carotid artery intima-media thickness, which could be used as an intermediate marker for the progression of atherosclerosis. The benefit of folate ingestion in reducing homocysteine levels is complicated by variations in the bioavailability of different folate isomers (variations in the length of the glutamate chain). Pooled analysis of all available observational data responding to well-defined criteria may be the best way to establish true relationships.

The traditional food additive safety assessment approach of establishing a 'no observed adverse effect level' (NOAEL) may not be appropriate for assessing the safety of whole foods, including functional foods. Whole foods are complex mixtures, and it is difficult to generate acute effects, as is expected with the NOAEL approach. Moreover, this approach is based on the assumption that no effect is the best outcome, but with functional foods, an actual effect — a beneficial one — is the expected outcome. Therefore, with functional foods the standard should be 'wholesomeness' rather than safety.

The EU Novel Food Directive sets out the principle of substantial equivalence based on a history of safe use, the standard that has been applied to foods historically. New foods should be evaluated against a reference food for composition, both nutritive and non-nutritive. It is not likely that routine safety assessment protocols can be developed for whole foods and food components. Consequently, the safety assessment will need to proceed on a case-by-case basis. Better understanding of the mechanisms underlying the action of foods and food components will make it possible to move away from the use of conventional safety factors.

*Consumer issues.* Sessions addressing consumer issues identified communication and consumer understanding as

**Table 1.** Biomarkers for well-being and disease risk reduction discussed at the meeting

Physical performance	Muscle glycogen, endurance time trial
Gut function	Gastrointestinal hormones, e.g. cholecystokinin; physical/chemical parameters, e.g. viscosity; biological responses, physiological responses, e.g. transit time
Immune function	Whole-body measures, e.g. delayed hyperactivity, vaccine response
Appetite control	Reduction in food intake, reduction in energy intake, hunger rating profiles
Cognitive function	No conceptual framework — need for markers that represent complexity of real-world decision making
Atherosclerosis	Blood pressure, LDL cholesterol, HDL cholesterol, intima-media thickness
Obesity	BMI, measures of fatness
Diabetes	Glucose tolerance, fasting blood glucose, insulin levels
Cancer	Recurrence of colon polyps, aberrant crypt foci
Bone health	Bone density, Ca kinetics

key factors for the success of functional foods. A first issue concerns the health claims that are justified and the level of scientific evidence needed to support such claims, and how can they be communicated effectively to the consumer. Second, the extent to which nutritionists understand the barriers to changing eating patterns has to be addressed. Pan-European surveys (e.g. the EU-funded HealthSense project) have shown that consumers have a good understanding of the link between diet and health and take the need for healthy eating seriously. Nevertheless, most consumers believe they do not need to change their diet because they feel it is healthy enough. In other words, consumers admit that a problem exists for society but not necessarily for them personally. Research reflects this by the fact that consumers rank the non-communicable chronic diseases as high concerns for society but as low concerns for themselves. Consumer perceptions of food safety issues constitute a third area of interest. Their perception of risk is a function of their own control, their possible benefit and the familiarity of the issue. Consequently, in terms of health impact, consumers tend to rank relatively unimportant or low-risk issues much higher than important or high-risk ones. For the consumer, risk is an emotional rather than a scientific issue, which suggests a mistrust of science and scientists. To improve the consumer's understanding of risk, the scientific community needs to better understand the consumer's perspectives in this respect.

#### *Session IV. The Future of Functional Foods*

Functional foods are a reality today and are likely to be so in the future. The key drivers behind functional food research and development are the food industry, consumers and governments. The progress of the science, particularly in the area of nutrition, is fundamental to the development of innovative food solutions for the improvement of key body functions and consequently consumer health. Past research has been strong in this field and has been able to develop sound and effective research programmes. In addition, the rapid development of the genomic sciences will allow us to improve our understanding of the effects of nutrients on gene function and health outcome and to predict individual nutritional needs. The fact that these new tools will have an impact on functional science is given; only the time frame is unpredictable. Overall, scientific research is focusing on the validation and use of biomarkers of functional improvement, the evaluation of the safety of foods and ingredients, the solid understanding of the mechanisms of action, and, of course, the discovery of bioactive ingredients.

Clearly, the success of functional foods is also dependent on the ability of the food industry to develop efficacious products that meet consumer needs. The global potential for functional foods is significant and growing because of increasing health consciousness and the self-care trends associated with ageing, knowledgeable and wealthier consumers. Today's consumer expects foods to be convenient, safe, healthy, and above all tasty. Functional foods in particular are expected to provide a credible health benefit beyond basic attributes to ensure

daily and future health. These health messages need to be communicated in a transparent, credible and understandable manner to the different stakeholders, including expert scientists with a consumer focus and the various opinion leaders, including health care providers, consumer organisations and the media.

In all of this, governments have a major role to play in the future of functional foods. They can create a favourable environment for basic and applied research programmes, promote continuous and truthful consumer education on nutrition science, facilitate integration of public health issues, competitive and innovative economic development with ethical and ecological perspectives, ensure the protection of consumers in the short and long term, and enforce regulatory systems for flexible and credible science-based claims on nutrition and health.

Finally, functional food science will create many opportunities, but its ultimate success and impact on public health will depend on the consumer's appreciation of products based on objective criteria like taste and convenience and subjective criteria like trust and credibility.

### **Conclusions**

The International Life Sciences Institute's (ILSI) international symposium on Functional Foods: Scientific and Global Perspectives provided an opportunity to address progress in this field since the first such international conference, which ILSI held in Singapore in 1995. Despite significant areas of controversy on functional foods, participants in the 2001 symposium agreed with Dr John Milner's statement that functional foods provide: 'an unprecedented opportunity to expand the use of food to improve health, decrease the risk of disease, and increase productivity'. The meeting participants also concurred that the ability to use claims was essential to the further development and success of functional foods.

The areas of disagreement are associated with the definition of the term 'functional foods' and with the standards of scientific evidence required to support health claims. Differences in definition include whether nutrients and non-nutrients are included, whether dietary supplements and even drugs are included, and whether functional foods should include only unprocessed foods or should also include enhanced or fortified foods. Across the world there are two distinctly different approaches to standards of evidence. Some countries are content with a culture or belief system approach based on history of use. Other countries rely on the paradigm of scientific substantiation that includes validated biomarkers. Such markers allow physiological responses to be measured in terms of improved well-being, enhanced function or reduction in disease risk.

Several important underlying concepts were addressed. First, a large amount of information is available, especially with the coming explosion of genetic marker information, but the translation of these individual pieces of information into knowledge is moving at a much slower pace. Second, there is a critical need to demonstrate valid and relevant health effects of functional foods and food components

in man. In this respect, a lack of validated biomarkers for specific health outcomes is a significant barrier to progress. Third, there is a need to better understand what normal physiological function is and what the range of normal variability is. Current work with single nucleotide polymorphisms is providing ever-expanding information about normal human genetic variability. However, this variability explains only a small amount of the risk associated with a specific change and, consequently, the difficulty of linking a specific health outcome to intake of a specific food or food component.

There are significant communication issues regarding functional foods that go beyond scientific understanding. Taste and convenience are still the primary reasons why

consumers choose specific foods, but there is a growing interest in self-administered health care. To develop credible and effective messages for consumers, there must be in-depth understanding of consumers' needs and wants and how they view the concept of functional foods and their consequent health benefits. This understanding is a prerequisite to generating behavioural change. The benefits of functional foods must be made accessible to both rich and poor. Most importantly, the food industry must do no harm in providing functional foods. To communicate the emerging scientific information to the consumer effectively, flexible science-based regulatory systems must be adopted by governmental institutions.