Consumption of functional food component

Markers of exposure to food component

Markers of target function / biological response

Markers of intermediate endpoint

Improved state of health and well-being or Reduced risk of disease

Health outcomes
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FUNCTIONAL FOODS

FROM SCIENCE TO HEALTH AND CLAIMS

by John Howlett

ILSI Europe
## CONTENTS

FOREWORD ......................................................................................................................................................................................... 1  
INTRODUCTION ............................................................................................................................................................................... 2  
HOW IS FOOD FUNCTIONALITY ASSESSED? ........................................................................................................................... 5  
WHERE CAN FUNCTIONAL FOODS PLAY A ROLE? .................................................................................................................... 6  
DELIVERING THE BENEFITS ......................................................................................................................................................... 24  
COMMUNICATING THE BENEFITS ............................................................................................................................................. 26  
FUTURE PERSPECTIVES .................................................................................................................................................................. 30  
GLOSSARY ......................................................................................................................................................................................... 32  
FURTHER READING AND REFERENCES ................................................................................................................................... 34

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“Let your food be your medicine” said Hippocrates. It is time now to revisit the concept of foods, beyond basic nutritional needs. Today, food has indeed become central for the cultural pleasure of feeding a family and greeting friends in a social setting.

Are foods also medicine? Products intended to cure diseases are medicinal products and not foods. But on the other hand, a healthy diet consisting of foods with functional properties can help promote well-being and even reduce the risk of developing certain diseases. WHO stresses the importance of a healthy diet in preventing non-communicable diseases. However, a diet can only be healthy if the combination of individual foods is good. Moreover, a healthy diet is not just about limiting certain components of concern such as saturated or trans fatty acids or simply delivering nutrient intake, it is also about including those elements that may provide an extra benefit.

Above all, eating should be a pleasurable experience and is often celebrated as a social event, helping communication and maintaining relations with family members and friends. Why not combine pleasure and functionality then? To keep alert when you have to work late at night, why not enjoy some food or drink that at the same time helps keeping you alert? To promote a healthy bowel function, why not integrate the goodness of dietary fibre into your daily food? To help prevent cardiovascular disease, why not naturally incorporate the preventive elements into your daily diet? We all eat many different foods every day; lets make sure we eat what suits us best for any particular need we have at that time, or what will promote our overall health in the long run.

It is easy to say: ‘eat healthy’, but do we really know what is the best food for a particular need? What type of evidence do we need to have? It is certainly not enough to study certain parameters simply because we are able to measure them. Rather we need to ensure that the parameters we use to measure health are really valid and relevant biomarkers for the target functions we are interested in. This is where functional food science can help by providing the tools to answer some of these questions.

This concise monograph provides an outline about the science and role of functional foods. First of all it describes what is meant by the term functional food, then looks at how functional foods are assessed and how they can play a role in a healthy diet. Additionally it summarises the technological aspects as well as the communication to consumers. Finally the monograph looks at the future perspective of foods beyond basic nutrition and the role of “omics” in exploring the benefits.

The reader will learn that physiological functionality of foods may have a bright future and can make a difference to help people eat better and healthier. Nevertheless, from a scientific or research point of view, and to paraphrase Winston Churchill, this is the end of the beginning and not the beginning of the end.

Thomas Hatzold
Kraft Foods
**INTRODUCTION**

**Lifestyle, diet & physical activity**

Human societies have become less rural and more urban and economic activity has become proportionally less agricultural and more industrially based. These changes have brought benefits in terms of improvements in many aspects of quality of life and health and they have also brought changes to the way individuals interact, the amount of leisure time they have, their access to food and their levels of physical activity. In developed countries improvements in the quality of life, not the least of which is a safer, more varied diet, are associated with increased and increasing longevity. In general, individuals have more leisure time, they have greater access to a wider variety of foods and their daily routine requires less physical activity. These changes, however, have made it increasingly difficult to balance energy intake and expenditure, resulting in increased frequency of overweight and obesity worldwide.

As these changes have taken place, there has been an increase in the prevalence of chronic, non-communicable diseases such as increased blood pressure, cardiovascular disease and type 2 diabetes. It is clear that aspects of lifestyle, diet and physical inactivity all play a role in the increasing incidence of these diseases and the success of measures to reduce them will depend on striking the right balance between these three factors. This has led to a realisation that diet can contribute to long-term health in ways that have not been recognised previously and this is leading to an appreciation of ways in which foods can bring positive influences to health and well-being beyond simply providing basic nutrition.

**History and the concept of a balanced diet**

Through much of its history, nutrition has concerned itself with the observation that deficiencies in the diet lead to disease states and that deficiency diseases can be avoided by ensuring an adequate intake of the relevant dietary components. For the first half of the twentieth century the focus of nutrition science was on establishing the minimum requirements for essential nutrients that ensure the avoidance of deficiency diseases. This led to the establishment of reference values, such as dietary reference intakes (DRIs), population reference intakes (PRIs), and dietary reference values (DRVs), for vitamins, minerals, proteins, fats, carbohydrates and energy. These guide strategies for nutrition policy and practice directed to ensuring that intakes are adequate to meet the needs of the average, healthy consumer for normal growth and development, body maintenance and physical activity. The concept of a balanced diet evolved, in which the ideal diet consisted of a sufficient variety of food groups (fruit, vegetables, cereals, meat, fish, dairy products etc.) to meet these target intake values for the essential nutrients.

The concept of a balanced diet has further evolved to embrace the need for dietary intakes to accommodate changes in lifestyles with correspondingly reduced energy expenditure and caloric needs, but with a continuing unaltered level of need for other key nutrients. There is a need to strike a balance in selecting a sufficiently varied choice of foods to ensure an adequate intake of essential nutrients, while avoiding excessive intakes of energy and the associated diseases. Increasing longevity increases the risk of developing non-communicable diseases if the balance of lifestyle, diet and physical activity is disturbed.
The selection of a balanced diet, which provides adequate intakes of nutrients while keeping energy intake in balance with basic metabolism and physical activity, remains the cornerstone of sound nutrition. Thus, there is a need to ensure the availability of diets and foods with appropriately increased amounts of nutrients relative to energy (that is, foods with an appropriate nutrient density). This need can be met by selection of natural products, but the lifestyle and the expectations of modern living do not make this easy and, as a result, opportunities have arisen for manufactured foods that meet these requirements. Concomitantly, an improved appreciation of the potential beneficial or adverse effects of nutrients and other components in the diet has led to the realisation that it is possible to create food items with specific characteristics that are capable of influencing body function over and above meeting the basic nutrition needs. These foods have come to be known as “functional”. Although of course at some level all foods are functional, these foods would additionally have the potential to promote long-term health, improving both physical and mental health and well-being.

**Food functionality: defining the concept**

The first systematic exploration of the positive aspects of food functionality was undertaken in Japan. Research programmes funded by the Japanese government during the 1980s focussed on the ability of some foods to influence physiological functions. This led, in 1991, to the definition in Japanese law of a category of “foods for special dietary use”, which were allowed to carry claims for specific health effects on their labelling. The claims had to be substantiated in order to receive the approval of the Japanese Ministry of Health and Welfare, and the foods could then be designated as “Foods for Specified Health Use” (FOSHU – Box 1).

**BOX 1**

Japan
Foods for Specified Health Use (FOSHU)

- Exert a health or physiological effect
- Have the form of ordinary foods (not pills or capsules)
- Consumed as part of an ordinary diet

In the latter half of the 1990s, the European Commission funded an activity to establish a science-based approach to exploring the concept of functional foods. This Concerted Action, “Functional Food Science in Europe” (FUFOSE), involved a large number of European experts in nutrition and related sciences and produced a consensus report that has become widely used as a basis for discussion and further evolution of thinking on the topic.

FUFOSE developed a working definition of a functional food as one that is “satisfactorily demonstrated to affect beneficially one or more target functions in the body, beyond adequate nutritional effects, in a way that is relevant to either an improved state of health and well-being and/or reduction of risk of disease” (Box 2). In the context of this working definition, a “target function” is a biological activity ongoing in the body that is a target for intervention with a view to the maintenance or improvement of health and well-being and/or reduction of risk of disease.
From a practical point of view, a functional food can be:

- A natural, unmodified food
- A food in which one of the components has been enhanced through special growing conditions, breeding or biotechnological means
- A food to which a component has been added to provide benefits
- A food from which a component has been removed by technological or biotechnological means so that the food provides benefits not otherwise available
- A food in which a component has been replaced by an alternative component with favourable properties
- A food in which a component has been modified by enzymatic, chemical or technological means to provide a benefit
- A food in which the bioavailability of a component has been modified
- A combination of any of the above.

However the functional food may be constituted (whether modified or not), it has to comply with the general requirement that it must be safe. In any discussion of food functionality, in either a regulatory or a scientific context, there is no consideration of a trade-off between health benefit and health risk. Whether a food is considered to be functional or not, it must always be safe for its intended use.
HOW IS FOOD FUNCTIONALITY ASSESSED?

A direct measurement of the effect a food has on health and well-being and/or reduction of disease risk is often not possible. This may be because the endpoint (the state of health and well-being) does not always lend itself to quantifiable measurement. Also, in the case of a disease like cancer, the time frame for development of the disease is very long or it would be unethical to monitor its development under the conditions of a controlled study.

Instead, functional food science works from knowledge of the key processes in the attainment of optimal health or in the development of a disease to identify markers that can be used to monitor how those key processes are influenced by foods or food components. Provided that the role of those key processes in the attainment of optimal health or disease development is well established and the markers are chosen accurately to reflect the process, it is possible to study the effect of consuming the food on the final endpoint (the improved state of health or reduction of disease risk) by measurement of the markers. The markers could be chosen to reflect either some key biological function (markers of a target function) or a key stage in development that is unequivocally linked to the endpoint under study, in which case they serve as markers of an intermediate endpoint (Figure 1). Measurements made in the short term on carefully chosen markers of intermediate endpoints can be used to make inferences about effects on final endpoints that would only otherwise be accessible through long-term study. Where the underlying target functions or intermediate endpoints are unequivocally linked to the risk of disease, the markers are also referred to as risk factors for the disease.

FIGURE 1

Functional Food Science in Europe

The use of markers to link food consumption to health outcome

Consumption of functional food component

Markers of exposure to food component

Markers of target function / biological response

Markers of intermediate endpoint

Improved state of health and well-being

or

Reduced risk of disease
A further Concerted Action (PASSCLAIM: Process for the Assessment of Scientific Support for Claims on Foods) drew on contemporary science and metabolic insight to explore the strategic use of markers to enable experimental evaluation of functional effects, ultimately with a view to their use in providing a scientific justification for claims relating to food functionality (see “How are claims to be substantiated?” page 27).

WHERE CAN FUNCTIONAL FOODS PLAY A ROLE?

The FUFOSE and PASSCLAIM activities reviewed several aspects of human health and well-being from the perspective of the availability of target functions that might be susceptible to dietary influence. The concept was tested and evaluated to provide an initial characterisation of the evidence-base supporting innovation and the development of functional foods, and any claims associated with them. Some of these are discussed below in order to illustrate the concept of food functionality:

- Early development and growth
- Regulation of energy balance and body weight
- Cardiovascular function
- Defence against oxidative stress
- Intestinal function – the gut microflora
- Mental state and performance
- Physical performance and fitness.

A short illustrative explanation of each topic is given, followed by a summary of some potential functional food components that have been, or might be, developed to improve health in each area. This list is not exhaustive and other areas of physiology also have potential for the development of functional foods. Also, examples of food components are given to illustrate the general nature of possible candidates. In many cases, further research is needed to confirm unequivocally whether or not they are able to fulfil their potential.
Early development and growth

The feeding of mothers during pregnancy and lactation and of their infants and young children is of great biological importance. Nutritional factors during early development may have not only short-term effects on growth, body composition and body functions but may also exert longer-term effects. The development of high blood pressure and heart disease, for example, can be affected by early nutrition – a phenomenon called “metabolic programming”. The interaction of nutrients and gene expression may form the basis for many of these programming effects and offers exciting potential for functional food development.

The course of pregnancy and childbirth, as well as the composition of breast milk and the short- and long-term development of the child, are influenced by the intake of nutrients, particularly polyunsaturated fatty acids (PUFA), folic acid, iron, zinc and iodine, as well as by total energy intake.

The evaluation of dietary effects on child growth may require epidemiological studies, as well as the evaluation of specific cell and tissue growth. Growth factors and conditionally essential nutrients (e.g. amino acids and polyunsaturated fatty acids – PUFAs) may be useful as ingredients in functional foods. Intestinal growth, maturation and adaptation, as well as longer-term function, may be influenced by food ingredients such as probiotics and oligosaccharides that function as prebiotics.

Pregnancy and the first postnatal months are critical periods for the growth and development of the human nervous system, processes for which adequate nutritional supplies are essential. Early diet may have long-term effects on some sensory and cognitive abilities, as well as behaviour. Possible long-term effects of early exposure to tastes and flavours on later food choice preferences could have an impact on public health.

Exciting possibilities have been suggested by the beneficial effects of some functional foods on the developing immune response, for example the effects of antioxidant vitamins, trace elements, fatty acids, L-arginine, nucleotides, pro-, pre- and synbiotics (see “Intestinal function”), and altered allergenic components of infant foods.

Peak bone mass at the end of adolescence can be increased by dietary means. This is expected to be of importance for reducing the risk of osteoporosis in later life. The combined effects of calcium and prebiotic fructans, together with other constituents of growing bone, such as proteins, phosphorus, magnesium and zinc, as well as vitamins D and K and fluoride, offer many possibilities for the development of functional foods, although many still need to be confirmed by research.

Some examples of opportunities for modulation of target functions related to growth, development and differentiation, and the food components that might be used to achieve them, are provided in Table 1.
### TABLE 1

Examples of opportunities for modulation of target functions related to growth, development and differentiation by candidate food components

<table>
<thead>
<tr>
<th>Target functions</th>
<th>Possible markers/measurement techniques</th>
<th>Candidate food components</th>
</tr>
</thead>
</table>
| Maternal adaptation during pregnancy and lactation   | Maternal weight  
Body fat  
Infant birth weight  
Duration of gestation (prematurity)  
Milk volume and quality | Micronutrients  
n-3 and n-6 PUFA  
Energy  
Protein |
| Skeletal development                                  | Ultrasound measurements  
Anthropomorphic measurements  
Bone mineral density | Calcium  
Vitamin D  
Vitamin K  
Prebiotics |
| Neural tube development                               | Ultrasound measurements | Folic acid |
| Growth and body composition                           | Anthropometry  
Body fat mass  
Total body water  
Procollagen propeptide excretion  
Urinary creatinine excretion | Essential amino acids  
Unsaturated fatty acids |
| Immune function                                       | Cellular and non-cellular immune markers  
Resistance to infection  
Response to immunisation | Vitamin A  
Vitamin D  
Antioxidant vitamins  
n-3 and n-6 PUFA  
Trace elements  
Zinc  
L-arginine  
Nucleotides and nucleosides  
Probiotics and prebiotics  
Neutral and acidic oligosaccharides |
| Psychomotor and cognitive development                 | Tests of development, behaviour, cognitive function, and visual acuity  
Electro-physiological measurements | n-3 and n-6 PUFA  
Iron  
Zinc  
Iodine |

Adapted from Diplock et al. (1999)
Regulation of energy balance and body weight

Dietary intakes and balance influence all metabolic and physiological processes. An optimally balanced diet is usually expressed in terms of its energy and content of macronutrients (carbohydrates, fats and proteins). Within these broad classes of macronutrients, there are sub-classes, which have differing nutritional impacts. Amongst the carbohydrates, a most important functional and metabolic distinction is between those that are digested and absorbed in the small intestine, for example, glucose, sucrose and available starch, and those that are not, for example, dietary fibres, resistant starch, sugar alcohols (polyols) and certain oligosaccharides. Amongst fatty acids, such distinctions depend on the length and saturation (that is the number of carbon atoms and whether adjacent carbon atoms are linked by double or single bonds) of their carbon chain. Thus, major functional components of lipids are saturated fatty acids (SFA) on the one hand, and monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) on the other.

Energy balance and obesity

Obesity is defined as an excessive accumulation of body fat. Its prevalence varies between 5% and 50% in different populations, depending on the definition applied. The epidemic of obesity with its accompanying health risks is now recognised to be one of the major health challenges in both the developed and developing world. People with central obesity are most at risk. Central obesity appears to be a reflection of increased amounts of internal (as opposed to subcutaneous) fat.

Obesity is associated with an increased risk of heart disease, type 2 diabetes, high blood pressure and some forms of cancer. The interaction of genetic predisposition and environmental factors, such as a sedentary lifestyle and a high-energy intake, is the most commonly accepted model for the cause of human obesity.

Diabetes

Diabetes mellitus is a disease characterised by inappropriately increased plasma glucose concentrations. Insulin is the main hormone that controls blood glucose levels, and diabetes results from impaired insulin secretion or reduced insulin action at its target sites (insulin resistance).

Two main forms of diabetes mellitus are defined by clinical manifestations and causes. Type 1 or insulin-dependent diabetes usually develops in young, lean individuals and is the result of an almost complete destruction of the pancreatic beta cells, usually as a consequence of an autoimmune process. Because it is the beta cells that produce insulin, type 1 diabetes is characterised by plasma insulin levels that are very low.

Type 2 or non-insulin-dependent diabetes usually develops in overweight and/or older individuals. It has a slow onset (the subject may be without clinical symptoms for several years) and is characterised by insulin resistance (reduced sensitivity of body tissues to insulin), resulting in chronically elevated plasma insulin and glucose levels.

Insulin resistance syndrome

Apart from being associated with higher than normal levels of insulin and glucose, insulin resistance is also associated with characteristic changes in lipid metabolism. Lipids, which are generally water-insoluble, are transported in the blood in the form of lipoprotein particles composed of specific proteins and lipids (triacylglycerol (TAG), cholesterol and phospholipids). Low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL) contain high concentrations of triacylglycerol (TAG) and cholesterol, and are termed “low density” on the basis of
comparison with the density of water. Elevated levels of LDL and VLDL are recognised risk factors for coronary and other cardiovascular diseases. High-density lipoproteins (HDL) contain lower concentrations of cholesterol and are believed to be beneficial. Insulin resistance syndrome is characterised by increased concentrations of TAG, decreased concentrations of HDL cholesterol, and high blood pressure.

Seen in association with central obesity as characterised, for example, by waist circumference and waist-to-hip ratio, this pattern of risk factors is also referred to as “metabolic syndrome”.

**Functional foods for optimising metabolism**

This area offers many opportunities for the development of functional foods. The approach to controlling glucose levels is based on choosing foods that cause a slower absorption of glucose into the bloodstream, so that blood glucose fluctuations are less pronounced and, consequently, insulin requirements are lowered. The rate of glucose uptake is influenced by the structural properties of foods, such as the presence of intact cells or starch granules. It is also influenced by the type of carbohydrate constituents, for example by certain types of oligosaccharides and starch, and by the content of soluble, viscous types of dietary fibre (pectin, gums, oat β-glucan and psyllium seed husk). Organic acids and other components are known also to influence the rate of glucose uptake.

The descriptor “low glycaemic index” is reserved for foods with carbohydrates that are absorbed in the gut but which cause only a slow and small rise in blood glucose levels. Examples of such foods are bread with whole grains and/or sour dough, legumes, whole grain pasta and products enriched in soluble viscous types of dietary fibre. Although the role of “low glycaemic foods” remains to be fully established, an increasing body of knowledge is becoming available in this area on which development of functional foods with optimised release of carbohydrates can be based.

Examples of opportunities for modulation of target functions related to the regulation of metabolic processes, and the food components which might be used to achieve them, are provided in Table 2.

**Cardiovascular function**

Cardiovascular diseases (CVD) are a group of degenerative diseases of the heart and blood circulatory system and include coronary heart disease (CHD), peripheral artery disease and stroke.

CHD is a major health problem in most industrialised countries and a rapidly emerging problem in developing countries and countries in transition. The predominant clinical pictures are angina (chest pain), myocardial infarction (heart attack), heart failure and sudden cardiac death. The arteries supplying blood to the heart are narrowed by atherosclerosis and may become suddenly blocked when an atherosclerotic plaque on the artery wall ruptures and is impacted by a blood clot. This leads to lack of oxygen to the heart muscle, damage to the heart muscle tissue and life-threatening loss of heart function.

To fully appreciate the potential role functional foods can play in the prevention of CVD, it is necessary to understand the diversity of risk factors associated with its development. These include high blood pressure, inflammation, inappropriate blood lipoprotein levels, insulin resistance (see the discussion under “Regulation of energy balance and body weight” above) and control of blood clot formation. The interdependence of these factors has not been fully characterised. Because only 50% of the incidence of CVD can be explained by these known
### Table 2

Examples of opportunities for modulation of target functions related to the regulation of metabolic processes by candidate food components

<table>
<thead>
<tr>
<th>Target functions</th>
<th>Possible markers</th>
<th>Candidate food components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintenance of desirable body weight</td>
<td>BMI, body fat content, anthropometric indices and imaging techniques as indirect measures of central obesity&lt;br&gt;Respiratory quotient&lt;br&gt;Resting metabolic rate</td>
<td>Reduced energy density&lt;br&gt;Fat and sugar replacers&lt;br&gt;Carbohydrate:fat ratio&lt;br&gt;Foods with low glycaemic index or response&lt;br&gt;Fibre&lt;br&gt;Polyols and other poorly-digestible carbohydrates</td>
</tr>
<tr>
<td>Control of blood glucose and insulin sensitivity</td>
<td>Fasting glucose&lt;br&gt;Postprandial glucose&lt;br&gt;Glucose tolerance test&lt;br&gt;Glycosylated haemoglobin&lt;br&gt;Measures of insulin dynamics&lt;br&gt;Fasting plasma insulin</td>
<td>As for body-weight maintenance plus:&lt;br&gt;Soluble viscous fibre&lt;br&gt;Reduction in saturated fatty acids</td>
</tr>
<tr>
<td>Control of TAG metabolism</td>
<td>Fasting plasma TAG&lt;br&gt;Postprandial plasma TAG</td>
<td>As for body-weight maintenance plus:&lt;br&gt;n-3 PUFA</td>
</tr>
<tr>
<td>Optimal performance during physical activity</td>
<td>Body temperature&lt;br&gt;Performance testing&lt;br&gt;Muscle mass&lt;br&gt;Muscle protein synthesis</td>
<td>Water/electrolytes&lt;br&gt;Energy&lt;br&gt;Carbohydrates with high and low glycaemic index or response&lt;br&gt;Ergogenic substances (e.g. creatinine)&lt;br&gt;Protein/specific amino acids&lt;br&gt;Caffeine</td>
</tr>
<tr>
<td>Fluid homeostasis</td>
<td>Water balance&lt;br&gt;Electrolyte balance</td>
<td>Isotonic carbohydrates&lt;br&gt;Electrolyte fluids</td>
</tr>
</tbody>
</table>

Adapted from Diplock et al. (1999)

Risk factors, other contributory and interactive factors are certainly involved. For example, genetic predispositions, smoking, and levels of physical activity play a role. Some specific examples of markers known to be risk factors for CVD follow.

**High blood pressure**

CVD is directly related to high blood pressure and any measures taken to reduce high blood pressure should lower the risk of coronary disease. High blood pressure increases the risk of arterial injury. Genetic predisposition
Concise Monograph Series

and obesity are involved in the aetiology of high blood pressure, but diet and lifestyle have a substantial impact, with overweight, physical inactivity, high sodium intake and low potassium intake being among the main contributors.

**Integrity of artery lining**

Damage to the endothelial cells that line the arteries, as well as more general structural damage at susceptible points in the arteries (such as at “forks”), increases the risk of CVD. Oxidation is now believed to be a major contributor to atherosclerosis, because it converts LDL into an oxidised form. Oxidised LDL has been found in damaged arterial walls and has been shown to have several actions that could contribute to the initiation and progression of arterial damage. The extent of LDL oxidation is related to the extent of atherosclerosis.

**Elevated blood lipids**

A raised plasma concentration of LDL is a strong risk factor for CVD. High levels of other lipoproteins, high TAG concentrations and low levels of HDL are also risk factors. Raised levels of lipids, especially TAG, after a meal appear to be a stronger risk factor than fasting levels.

**High homocysteine levels**

Epidemiological data suggest that high plasma levels of homocysteine, an amino acid, are associated with increased risk of CVD. Several mechanisms for the effects of homocysteine on atherosclerosis and thrombosis have been suggested, but none has been confirmed.

**Increased blood clot formation**

The control of blood clotting is likely to be an important element in the reduction of the risk of CVD. Risk factors include those that increase the clumping of platelets and those that increase the activity of the clotting factors. These are counterbalanced by factors that promote the breakdown of the clot.

**Functional foods to promote optimal heart health**

**Balance of dietary lipids**

The levels of blood lipids can be influenced by dietary fatty acids, an influence usually related to their molecular size and shape and the degree of saturation of their hydrocarbon chains.

Fatty acids with a hydrocarbon chain that contains no double bonds are saturated fatty acids (SFAs). SFAs with chain lengths of 12–16 carbon atoms increase plasma LDL cholesterol concentrations more than they increase plasma HDL concentrations. In their favour, they cannot become oxidised.

Unsaturated fatty acids are those in which the hydrocarbon chain contains at least one double bond. Monounsaturated fatty acids (MUFA) contain one double bond; PUFAs contain two or more. Most naturally occurring unsaturated fatty acids are cis-fatty acids, in which the two hydrogen atoms around the double bonds (one at each end) are positioned on the same side of the fatty acid chain. This causes a bend in the hydrocarbon chain at that point. In contrast, trans-fatty acids have the hydrogen atoms at each of the double bonds on opposite sides of the fatty acid chain and, as a result, are straight and more like SFAs. They are formed during some manufacturing processes and are therefore consumed in products such as
hard margarines and baked goods. They are also formed in the rumen of animals such as cows and, consequently, a portion of the trans-fatty acids in the diet (it has been estimated at around 20%) comes from the consumption of dairy products and meat. Dietary trans-unsaturated fatty acids can increase plasma LDL and reduce HDL cholesterol concentrations. Diets low in SFAs and trans-fatty acids could therefore reduce the risk of CVD.

Evidence suggests the possibility of protecting vascular integrity through beneficial modulation of risk indicators such as high plasma homocysteine concentrations and high blood pressure. Folate has the potential to reduce cardiovascular risk by lowering the plasma level of homocysteine. Evidence supports its ability to reduce homocysteine levels but, to date, its effectiveness in reducing CHD has not been confirmed in clinical trials.

An increase in the intake of potassium and calcium and a reduction in sodium can help to reduce blood pressure. Consumption of certain fatty acids (see above) and peptides derived from milk proteins has also been reported to be beneficial.

Two significant areas of functional food development are the use of plant sterol and stanol esters and soya protein to reduce levels of LDL cholesterol.

Plant sterols are natural constituents of plants, including trees and a number of common crops, such as soya and maize. They play a similar role to that of cholesterol in animals as a metabolic precursor and as a structural molecule. It has been known for 50 years that plant sterols can interact with cholesterol in the intestinal tract to bring about a reduction of cholesterol absorption and a subsequent reduction in blood cholesterol. More recently, a number of studies have confirmed the ability of plant sterols and stanols (their hydrogenated derivatives) to reduce LDL cholesterol under a variety of conditions. They are present naturally in the diet at levels below those shown by the studies to be necessary for effect. However, recent technological advances providing for the extraction and esterification of plant sterols, either as the sterols themselves or as stanols, allow them to be solubilised in the matrix of food fat and so to be incorporated easily into food products at effective levels.

The cis-unsaturated fatty acids with 18 carbon atoms – oleic (mono-unsaturated), linoleic and alpha-linolenic acids (polyunsaturated) – reduce plasma concentrations of LDL cholesterol and some may also raise plasma concentrations of HDL cholesterol. Functional foods enriched in these unsaturated fatty acids could also be used to reduce the risk of CVD. Like alpha-linolenic acid, the long-chain, highly unsaturated PUFAs found in fish oils belong to the n-3 family. They can promote improvements in endothelial and arterial integrity as well as counteract blood clotting and reduce blood pressure. They also reduce plasma TAG levels and may have suppressive effects on the cellular immune system. One of the focus areas of functional food development concerns the incorporation of n-3 fatty acids into foods.

Other food components with functionality for optimal heart health

Soluble viscous types of dietary fibre can reduce LDL cholesterol concentrations, particularly in people with high lipoprotein levels.

Diets rich in antioxidants, including plant flavonoids, can inhibit LDL oxidation and inhibit the formation of cell-to-cell adhesion factors, which are implicated in damage to the arterial endothelium and in the formation of blood clots. However, the importance of this for CVD remains to be established.
Defence against oxidative stress

Oxygen is essential to human life. Without it, we cannot survive. Paradoxically, oxygen is also involved in toxic reactions and, therefore, is a constant threat to the well-being of the human body.

Most of the potentially harmful effects of oxygen are believed to be the result of the formation and activity of reactive oxygen species (ROS). These act as oxidants and are believed to be major contributors to ageing and to many of the diseases associated with ageing, including cardiovascular diseases (CVD), cancer, cataracts, age-related decline in the immune system, and degenerative diseases of the nervous system, such as Parkinson’s and Alzheimer’s diseases.

The human body has several mechanisms for defence against ROS. The various defences are complementary to one another because they act on different oxidants or in different cellular compartments. One important line of defence is a system of antioxidant enzymes. Nutrition plays a key role in maintaining these enzymatic defences. Several essential minerals and trace elements, including selenium, copper, manganese and zinc, are involved in the structure or catalytic activity of these enzymes. If the supply of these is inadequate, enzymatic defences might be impaired.

Another line of defence is the group of small-molecular-weight compounds that act as antioxidants, examples are glutathione, and some vitamins (e.g. vitamins C and E), that regenerate the buffer capacity of the body’s antioxidant systems.

If exposure to external sources of oxidants is high, for example from tobacco smoke or atmospheric pollution, the body’s antioxidant defences may be put under pressure to cope. The result is a condition called oxidative stress, an imbalance between pro-oxidants and antioxidants. In the normal situation, pro-oxidant factors are adequately counterbalanced by antioxidant defences. An increase either in the production of oxidants or in a deficiency in the defence system could disturb this balance, causing oxidative stress.

Functional foods to promote optimal defence against oxidative stress

The body’s own defences could be supported by a wide variety of small-molecular-weight antioxidants found in the diet, and these give ample scope for functional food components. The best known are vitamin E, vitamin C, carotenoids and polyphenols, including flavonoids. Many of the antioxidant compounds in the diet are of plant origin. Plant leaves are exposed to visible and ultraviolet light and other radiation and are especially susceptible to damage by activated forms of oxygen. Hence, they contain numerous natural antioxidant constituents that can either counter ROS directly or boost the regeneration system to restore antioxidant capacity. Trials to date with single antioxidants have not provided evidence of effect. So, if an advantage is to be obtained, it might best come from consuming a battery of antioxidants such as occur naturally in foods.

Examples of opportunities for modulation of target functions related to defence against oxidative stress, and the food components that might be used to achieve them, are provided in Table 3.
The human large intestine (colon) is a highly metabolically active organ. The colon contains an extremely complex microbial ecosystem. In fact, bacterial cells account for around 90% of the total cells in the body. The majority of these bacteria are anaerobic (they die in the presence of oxygen). The most common species in the adult human colon are those of the bacteroides, bifidobacterium and eubacterium.

The gut microflora provides the basis for a barrier that prevents harmful bacteria from invading the GI tract. Moreover, it plays a major role in eliciting, at an early age, an immune system which has a measured response to foreign proteins as potential antigens, balanced with an effective resistance to infection. The intestinal microflora, together with the gut’s own immune system, allows the resident bacteria to perform a protective function, especially against the proliferation of pathogens. Both large bowel integrity and colonic microflora are important in determining stool characteristics, such as weight, consistency, frequency and total intestinal transit time – perhaps the most reliable markers of general colonic function. The composition and the metabolic and enzymatic activities of the faecal microflora, which may themselves be either beneficial or risk factors, can be good markers of the status of the resident gut microflora.

The infant’s colon is sterile at birth, and the organisms that make up the microflora are acquired during delivery and in subsequent days from the mother and the environment. The initial colonising species create a habitat that favours the growth of strict anaerobes. Thereafter, differences

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**TABLE 3**

Examples of opportunities for modulation of target functions related to defence against oxidative stress by candidate food components

<table>
<thead>
<tr>
<th>Target functions</th>
<th>Possible markers/measurement techniques</th>
<th>Candidate food components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preservation of structural and functional activity of DNA</td>
<td>Measurement of damaged DNA components</td>
<td>Combinations of vitamins E and C, carotenoids and polyphenols including flavonoids</td>
</tr>
<tr>
<td>Preservation of structural and functional activity of polyunsaturated fatty acids</td>
<td>Measurement of lipid hydroperoxides or derivatives</td>
<td>As above</td>
</tr>
<tr>
<td>Preservation of structural and functional activity of lipoproteins</td>
<td>Measurement of lipid hydroperoxides and oxidised apoproteins</td>
<td>As above</td>
</tr>
<tr>
<td>Preservation of structural and functional activity of proteins</td>
<td>Measurement of damaged proteins or components</td>
<td>As above</td>
</tr>
</tbody>
</table>

Taken from Diplock et al. (1999)
in the composition of the microflora are believed to depend largely on the nature of the diet as well as the host. The microflora of breast-fed infants is dominated by bifidobacteria. In contrast, formula-fed infants have a more complex gut microflora, which includes bifidobacteria, bacteroides, clostridia and streptococci. After weaning, a new adult-like equilibrium is set up, depending again on the host and diet. Each individual has his or her own specific gut microflora, which, in its uniqueness, is comparable to a fingerprint.

Bacterial numbers and composition vary considerably along the GI tract, but the large intestine is by far the most intensively populated part of the gut microbial ecosystem, with several hundred species accounting for a total of between $10^{11}$ and $10^{12}$ bacteria per gram of contents. Quantitatively, the most important genera of intestinal bacteria in humans are the bacteroides and the bifidobacteria, which can account for 35% and 25%, respectively, of the known species. Traditional gut microbiological methodologies are based on morphological and biochemical properties of the organisms. Because these methods rely on an ability to culture the organisms taken by sampling and not all the organisms present can be cultured, it is likely that there are many more species of bacteria present in the gut than have yet been identified. However, recent advances in molecular genetics for quantitative and qualitative monitoring of the nucleic acids from human gut microflora have revolutionised their characterisation and identification.

The different components of the colonic microflora exist in a delicate balance. Some bacteria are considered actively beneficial (e.g. bifidobacteria and lactobacilli), and others benign (e.g. certain eubacterium). Both types of bacteria are believed to suppress the growth of a third group of bacteria that are potentially harmful to human health. These harmful bacteria include the proteolytic bacteroides and clostridia, sulphate-reducing bacteria and the pathogenic species of the Enterobacteriaceae. Thus a symbiosis has evolved between the host and its gut microflora. Increasing evidence suggests that gastrointestinal (GI) well-being and function may be compromised by modern lifestyles (e.g. eating habits, antibiotic use, or stress) and that this is related to disturbances in gut microflora composition and function.

The main substrates for bacterial fermentation are dietary carbohydrates that have escaped digestion (i.e. dietary fibre) and endogenous carbohydrates (e.g. mucus). Dietary fibre includes starch that enters the colon (resistant starch), as well as non-starch polysaccharides (e.g. celluloses, hemicelluloses, pectins and gums), non-digestible carbohydrates (such as fructo- and galactooligosaccharides added as prebiotics, and polydextrose). In addition, proteins and amino acids can be used as growth substrates by colonic bacteria.

The main end products of fermentation in the colon are short-chain fatty acids (SCFA), such as acetic, propionic and butyric acids, which play various important metabolic roles. In particular, butyric acid is of importance for colonocyte health. In addition, the process of fermentation induces a number of changes in the metabolic environment of the gut lumen that are believed to be beneficial to health. These include a lowering of the pH (increased acidity), increase in faecal water, a decrease in the toxicity of the luminal contents and, sometimes, laxative properties including softening of faeces. A stimulation of colonic mineral absorption (magnesium, calcium) also has been reported.

The gut microflora is a complex interactive community of organisms, and its functions are a consequence of the combined activities of all the microbial components. It is commonly agreed that gut microflora can play an important role in GI infections, constipation, irritable bowel syndrome, inflammatory bowel diseases and, perhaps, colorectal cancer.
**Functional foods to promote gut health**

The gut is an obvious target for the development of functional foods, because it acts as an interface between the diet and all other body functions. One of the most promising areas for the development of functional food components lies in the use of probiotics and prebiotics to modify the composition and the metabolic activity of the gut microflora.

A probiotic is defined as a live microbial food ingredient that confers a health benefit on the consumer.

Various species of lactobacilli and bifidobacteria combined (or not) with *Streptococcus thermophilus* are the main bacteria used as probiotics in yoghurts or fermented dairy products. Their major health benefits, demonstrated in humans, are alleviation of lactose intolerance and reduction of the incidence or severity of GI infections. They have also been shown to reduce the incidence of precancerous lesions in carcinogen-treated animals, but clinical trials are needed to confirm the importance of this observation for humans. Because probiotic bacteria are only transient in the intestinal tract and do not become part of the host’s gut microflora, regular consumption is necessary for the maintenance of favourable effects.

One mechanism by which probiotic bacteria may promote health in the digestive tract is by altering the local immune response. Survival of bacteria during intestinal transit and adhesion to intestinal cells seem to be important for modifying the host’s immune reactivity. A favourable modification of immune responses is the likely explanation for the reduction seen in the risk of atopic disease in children after the ingestion of probiotics.

A prebiotic is a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or modifying the metabolic activity of one or a limited number of bacterial species already established in the colon that have the potential to improve host health. Key criteria for a food ingredient to be classified as a prebiotic are (i) that it must not be hydrolysed or absorbed in the upper part of the GI tract so that it reaches the colon in significant amounts, and (ii) it must be a selective substrate for one or more beneficial bacteria that are stimulated to grow. It may also induce local (in the colon) or systemic effects through bacterial fermentation products that are beneficial to host health.

Apart from their potential to modify the gut microflora and its metabolic activities in a beneficial manner, many other helpful effects of prebiotics are being investigated. These include their ability to modulate gut function and transit time, to activate the immune system, to increase the production of butyric and other short-chain fatty acids, to increase the absorption of minerals such as calcium and magnesium and to inhibit lesions that are precursors of adenomas and carcinomas. Thus, they could have the potential to help reduce some of the risk factors involved in the causes of colorectal diseases. Strategies for developing prebiotic products as functional foods aim to provide specific fermentable substrates for bacteria such as bifidobacteria and lactobacilli. These may provide beneficial amounts and proportions of fermentation products, especially in the lower part of the colon where the effects are believed to be most favourable.

Mixtures of probiotics and prebiotics, which favourably modify the gut flora and its metabolism by increasing the survival of health-promoting bacteria, are described as synbiotics.
The major applications for probiotics are in dairy foods. Prebiotics are added to dairy products, table spreads, baked goods and breads, breakfast cereals and bars, salad dressings, meat products and some confectionery items.

Examples of opportunities for modulation of target functions related to intestinal physiology, and the food components that might be used to achieve them, are provided in Table 4.

### Mental state and performance

Some effects of foods or food components are not directly related to disease or health in the traditional sense but they, nevertheless, fulfil an important function in changing mood or mental state. Such changes may affect appetite or the sensation of satiety, cognitive performance, mood and vitality, and an individual’s reaction to stress, with consequent changes in behaviour.

Behaviour is probably the most varied and complex of all human responses. This is because it is the cumulative outcome of two distinct influences: (i) biological factors, including genetics, gender, age, body-mass, etc., and

### TABLE 4

Examples of opportunities for modulation of target functions related to intestinal physiology by candidate food components

<table>
<thead>
<tr>
<th>Target functions</th>
<th>Possible markers</th>
<th>Candidate food components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal intestinal function and stool formation</td>
<td>stool consistency and form</td>
<td>Non- and poorly-digestible carbohydrates</td>
</tr>
<tr>
<td></td>
<td>stool weight</td>
<td>Probiotics, prebiotics and synbiotics</td>
</tr>
<tr>
<td></td>
<td>stool frequency</td>
<td></td>
</tr>
<tr>
<td></td>
<td>gut transit time</td>
<td></td>
</tr>
<tr>
<td>Colonic microflora composition</td>
<td>microflora composition</td>
<td>Non- and poorly-digestible carbohydrates</td>
</tr>
<tr>
<td></td>
<td>enzyme/metabolic activities</td>
<td>Probiotics, prebiotics and synbiotics</td>
</tr>
<tr>
<td>Control of gut-associated lymphoid tissue (GALT) function</td>
<td>immunoglobulin A secretion</td>
<td>Probiotics</td>
</tr>
<tr>
<td></td>
<td>cytokines</td>
<td>Prebiotics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Synbiotics</td>
</tr>
<tr>
<td>Control of fermentation products</td>
<td>short-chain fatty acids</td>
<td>Non- and poorly-digestible carbohydrates</td>
</tr>
<tr>
<td></td>
<td>gas ($H_2$, $H_2S$)</td>
<td>Prebiotics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Synbiotics</td>
</tr>
<tr>
<td>Gut epithelial integrity</td>
<td>cellular markers</td>
<td>Non- and poorly-digestible carbohydrates</td>
</tr>
<tr>
<td></td>
<td>mucosal enzymes</td>
<td>Prebiotics</td>
</tr>
<tr>
<td></td>
<td>redox status</td>
<td>Synbiotics</td>
</tr>
</tbody>
</table>

Adapted from Diplock et al. (1999)
(ii) socio-cultural aspects, including tradition, education, religion, economic status, etc. As a result, perceptions about the effects of food components on behaviour and mental performance are characterised by a high degree of subjectivity, with large differences in response among people. Age, weight and sex are among a number of crucial parameters to take into account when evaluating the power of food components to alter behaviour. In addition, the effects seen immediately after the first time a food component is ingested may be different from the longer-term effects of the same food component as a part of the habitual diet. In some cases, adaptation may occur so that with repeated ingestion the effects may be diminished or lost.

Key aspects of behaviour that may be affected by foods include performance in mental functions (such as vigilance, memory, attention and reaction time) and aspects of eating behaviour (such as eating frequency, food preferences and dietary selection). In general, two types of effects can be discriminated: (i) the immediate effects, such as those on reaction time, attention focus, appetite and satiety, and short-term effects on memory; and (ii) longer-term effects, such as changes in memory and mental processes in ageing. Adaptation effects may be a crucial consideration in the case of agents that are used to modify appetite (palatability enhancers, artificial flavours, colours, etc.) and satiety (e.g. fibre, carbohydrate and protein content) over long periods where the aim is to assist in weight control.

Functional foods to promote optimal mental performance

Some functional foods – such as the ideal lunch food that will not induce, or might even prevent, a dip in vigilance in the post-lunch period – are desirable to everyone. Other foods could be functional for students who want to face exams with the maximum intellectual readiness; for those people at an emotional low point who expect to obtain a lift by ingesting foods such as chocolate, sugars or alcohol; or for the elderly and others who may have failing memory. In considering functional foods to promote optimal mental performance, the specific needs of the target consumer are of key importance.

Glucose has been reported to exert general beneficial influences on mental performance, including improvements in working memory and decision time, faster information processing and better word recall. Caffeine also can lead to an improvement in most measures of cognitive performance (reaction time, vigilance, memory and psychomotor performance), especially in the morning hours.

Meals high in carbohydrate help to produce feelings of sleepiness and calmness. In addition, the amino acid tryptophan reduces sleep latency. Tyrosine and tryptophan may help in recovery from jet lag, but only a limited amount of scientific evidence supports this effect.

Sweet foods, such as sucrose, may relieve distress in young infants and may reduce pain perception in members of the general population.

Meals high in protein reduce hunger and increase satiety, which may help in body weight control.

Intake of alcohol is both traditional and widespread in Europe. It is one of the few substances to affect all major areas of psychological and behavioural functions (appetite, cognitive performance, mood and stress), and the effects are conspicuously dependent on the dose.

Examples of opportunities for modulation of target functions related to behaviour and mental performance, and the food components that might be used to achieve them, are provided in Table 5.
### TABLE 5

Examples of opportunities for modulation of target functions related to behaviour and mental performance by candidate food components

<table>
<thead>
<tr>
<th>Target functions</th>
<th>Possible markers</th>
<th>Candidate food components</th>
</tr>
</thead>
<tbody>
<tr>
<td>Appetite, satiety and satiation</td>
<td>Direct measurement of food intake</td>
<td>Protein, Fat replacers, Fat substitutes, Sugar substitutes, Structured fats, Specific fatty acids, Dietary fibre and non-digestible oligosaccharides</td>
</tr>
<tr>
<td></td>
<td>Indirect measurement of food intake</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Subjective ratings of appetite and hunger</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Satiety-related hormones, peptides and molecular markers</td>
<td></td>
</tr>
<tr>
<td>Cognitive performance</td>
<td>Objective performance tests</td>
<td>Glucose, Low and high glycaemic carbohydrates, Caffeine, B vitamins, Choline</td>
</tr>
<tr>
<td></td>
<td>Standardised mental function tests</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Interactive games</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Multifunction tests</td>
<td></td>
</tr>
<tr>
<td>Mood and vitality</td>
<td>Quality and length of sleep</td>
<td>Alcohol, Low and high glycaemic carbohydrates, Carbohydrate:protein ratio, Tyrosine and tryptophan</td>
</tr>
<tr>
<td></td>
<td>Attitudes (questionnaires)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Standardised mental function tests</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ratings of subjective states</td>
<td></td>
</tr>
<tr>
<td>Stress (distress) management</td>
<td>Blood pressure</td>
<td>Alcohol, Sucrose</td>
</tr>
<tr>
<td></td>
<td>Blood catecholamines</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Blood opioids</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Skin electrical impedance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Heart rate continuous monitoring</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Diplock et al. (1999)
Physical performance and fitness

During physical stress such as exercise, demands are high for food components (the substrates) that act as the starting material for reactions that release energy. Diet can play a crucial role in improving the level of performance.

Training and competition will increase the daily energy expenditure by between 500 and 1000 kilocalories per hour of exercise, depending on intensity. Large sweat losses may pose a risk to health by inducing severe dehydration, impaired blood circulation and heat transfer. This may ultimately lead to heat exhaustion and collapse. Insufficient replacement of carbohydrates may lead to low blood glucose levels, fatigue and exhaustion.

An ever-increasing amount of daily, high-intensity training leads to high stress on the metabolic machinery – the musculoskeletal and hormonal systems. A growing body of evidence supports observations that the supply of food ingredients or food-derived substances may interact with the biochemical and physiological systems involved with physical and mental performance. The results may impact recovery from intensive training and, hence, affect the physical well-being and health of the athlete.

Functional foods to promote optimal physical performance and recovery

Requirements for specific nutrients and water depend on the type, intensity and duration of physical effort. Specific nutritional measures and dietary interventions can be devised to be appropriate for the distinct phases of preparation, competition and recuperation.

Oral rehydration products for athletes were one of the first categories of functional foods and drinks for which scientific evidence was obtained on all levels of functionality. Among these functions are rapid gastric emptying, fast intestinal absorption, improved water retention, improved thermal regulation, improved physical performance and delayed fatigue.

Liquid food formulae, established to deliver fluid and available carbohydrates and electrolytes in a convenient and easily digestible form, have been shown to be of benefit to athletes. Exercise-induced losses of nitrogen, minerals, vitamins and trace elements should be replenished by ingesting larger amounts of high quality, micronutrient-dense foods at meal times. However, this may be difficult in those circumstances in which low-energy diets are combined with intense training or in the case of multiple-day events, such as cycling competitions.

The use of special meals or food products and micronutrient supplementation can help ensure adequate intakes under these conditions. Specific types of carbohydrates with moderate-to-high glycaemic index in combination with each other and with protein have been shown to influence physical performance and enhance recovery of athletes, and this offers potential for the development of functional foods.

Some further considerations

The significance of risk factors

In the preceding discussion, risk factors for various diseases have been used to identify where functional foods might be used to beneficially affect health and, specifically, to reduce the risk of disease. While any particular risk factor may present a suitable target for change by a functional food, it has to be borne in mind that diseases are the end result of complex biological processes. Many factors may contribute to the establishment of a disease, either acting together or independently through multiple pathways. Although it may be possible significantly to influence any one risk factor by the consumption of a functional food, that alone may not reduce the overall risk that the disease...
will eventually become established. In order to achieve an actual reduction in the incidence of the disease, it may be necessary to influence simultaneously several risk factors in a positive way.

Similarly an optimal state of health and well-being is the outcome of a balance of complex biological processes. Its maintenance will most likely be achieved by seeking to influence several target functions in a positive way in concert.

The assessment of food functionality can be simplified by considering the impact of food components on single risk factors and target functions. However, in reality, the interaction between risk factors and between the underlying processes, represented by target functions,

---

**FIGURE 2**

*Multiple pathways to health outcomes*

- Consumption of functional food component
- Markers of exposure to food component
- Markers of target function / biological response
- Markers of intermediate endpoint
- Improved state of health and well-being or Reduced risk of disease

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provides multiple pathways for achieving a reduced risk of disease and an improved state of health and well-being in which a spectrum of functional foods is eaten as part of a broad and balanced diet (Figure 2).

**Functional foods and drugs**

Functional foods are not medicines. Although they are intended to modify physiological functions within the body in a positive way, their mode of action is to restore, reinforce or maintain normal body processes in ways consistent with normal physiology. They may restore or enhance body functions within normal ranges in order to optimise health and well-being or they may reduce factors known to be associated with the risk of contracting diseases. Medicines on the other hand function by intervening in disturbed physiological processes or by amplifying physiological processes beyond normal extremes in order to achieve an effect. Their function is to treat or prevent diseases, or to heighten physiological performance outside the normal range. However, there is no absolute boundary between foods and drugs in terms of their functionality. The distinction has to be made case by case, taking into account the type of product (food, supplement or pill) and its effect.

As a general rule, functional foods are intended to be consumed as part of a normal diet and they take the form of foods. Medicines are intended to be taken as part of a controlled regimen, often under the supervision of a medical practitioner, and they usually take the form of tablets, pills, capsules or syrups, which can be administered in precise doses. Ultimately, the manufacture and marketing of medicines is subject to different regulatory controls than those that apply to the manufacture and marketing of foods. Functional foods fall within the control of the food legislation. Some characteristics of functional foods and medicines are listed in Box 3. The list is not exhaustive or definitive. It is intended only to be indicative of the differences between them.

Food supplements, like medicines, often take the form of pills or capsules but they cannot legally be presented as treating or preventing diseases, and they are controlled by food law. Although from a legal perspective they are foods, they do not usually have the form of foods and are not consumed in the same way as typical foods as part of the normal diet. Consequently they do not fall within the concept of functional foods as presented and discussed in this monograph (see Box 1 and Box 2).

### BOX 3

**Some differences between functional foods and medicines**

<table>
<thead>
<tr>
<th></th>
<th><strong>Functional food</strong></th>
<th><strong>Medicine</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mode of action</strong></td>
<td>Modulation of a physiological process within the normal range</td>
<td>Intervention in a disturbed physiological process, or modulation of a physiological process outside the normal range</td>
</tr>
<tr>
<td><strong>Purpose</strong></td>
<td>To restore or enhance normal function in order to optimise health, well-being and performance</td>
<td>To treat or prevent disease, To enhance performance beyond normal range</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Food, consumed as part of the normal diet</td>
<td>Pill, tablet, capsule or syrup taken in controlled dose according to a timetable</td>
</tr>
</tbody>
</table>
Technology, in the form of food processing, is an established part of the food chain. It serves to convert raw materials into edible, safe and nutritious food with the taste and texture, shelf life and convenience to suit everyday needs. Technology also provides the means to extract components with functionality from foods and raw materials and to optimise their form and chemical structure to make them suitable for inclusion in new food products. The extraction of phytosterols from plant sources and their esterification, either as sterols or in hydrogenated form as stanols, to enable them to be incorporated into products for use in reducing serum LDL-cholesterol (described above) provides an example of this. As more food components with the desired functionality are identified, technology has the potential to maximise their accessibility and availability so that they become available on an everyday basis in a form that suits consumers’ needs and preferences.

Technology can help to achieve this goal in three ways:
• By creating new functional food components in traditional materials, in new raw materials or by synthesising
• By maximising the presence of functional food components already existing in foods and raw materials by improving their preservation, modifying their function or increasing their bioavailability
• By providing the means to monitor the amount and effectiveness of functional components in foods and raw materials to ensure that they are retained to the maximum degree at all stages in the food chain

Some examples of the technological tools available to meet these aims are summarised in Table 6.
**TABLE 6**

Examples of technological challenges, with possible solutions and examples of applications, to optimise functional food components

<table>
<thead>
<tr>
<th>Technological challenges</th>
<th>Possible technological solutions</th>
<th>Examples of applications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creation of functional components from raw materials and by <em>de novo</em> synthesis</td>
<td>Immobilised enzyme systems</td>
<td>Bioactive peptides</td>
</tr>
<tr>
<td></td>
<td>Membrane processes</td>
<td>Novel carbohydrates</td>
</tr>
<tr>
<td></td>
<td>Chemical modification</td>
<td>Phytochemicals</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Antioxidants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Minerals</td>
</tr>
<tr>
<td>Optimisation of functional food components by increasing their concentrations in raw materials</td>
<td>Fermentation, enzyme technologies</td>
<td>Minerals</td>
</tr>
<tr>
<td></td>
<td>Non-thermal processes (e.g. high pressure)</td>
<td>Antioxidants</td>
</tr>
<tr>
<td>Optimisation of functional food components through their modification</td>
<td>Tailored enzymatic processes</td>
<td>Oligosaccharides as fat replacers</td>
</tr>
<tr>
<td>Optimisation of functional food components through increased bioavailability</td>
<td>Fermentation technologies</td>
<td>Micro-organisms</td>
</tr>
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<td>Membrane permeabilisation processes (e.g. enzymes, electric field pulses)</td>
<td>Minerals</td>
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<td>Vitamins</td>
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<td>Optimisation of functional components in raw materials and foods through maximal retention</td>
<td>Encapsulation processes</td>
<td>Micro-organisms</td>
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<td>Sphere packaging technologies</td>
<td>Bioactive peptides</td>
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<td>Minerals</td>
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<td>Monitoring the production of functional foods and functional components</td>
<td>Sensors/markers</td>
<td>Micro-organisms</td>
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<td>Carbohydrates</td>
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Adapted from Diplock *et al.* (1999)
COMMUNICATING THE BENEFITS

How do consumers learn about the health benefits of functional foods?

Functional foods and food components may be available in the marketplace but in order for consumers to access the benefits of functional foods, they must be informed about them. The simplest and most direct way for consumers to learn about functional foods is through food labelling but the information provided by labelling must be understandable and it must be reliable.

General food labelling laws already in place almost everywhere require that information provided on food labels and through advertising is factually truthful and not misleading. For the most part, these general laws are sufficient to ensure that statements made on labels and in advertisements properly and adequately convey information to consumers. However, in the case of claims made about the health benefits of foods there is extra scope for confusion and uncertainty. Firstly, this scope for confusion arises because of the potential overlap between foods conveying health benefits and medicines. Secondly, a full understanding of the meaning and underlying bases of health claims usually requires expert knowledge.

The first source of possible confusion has been resolved historically by legislation to prevent health claims being made about foods; such claims may only be made for medicines and are controlled by legislation concerning medicines. Recently this situation has changed (and continues to evolve) with categories of health claims being permitted for foods in various countries. These are subject to a clear distinction being made between health benefits relating to support or enhancement for normal body functions and reduced risk of disease (in the case of foods), and the treatment or prevention of disease (in the case of medicines).

Legislators have sought to resolve the second source of possible confusion, the need for expert knowledge, by requiring health claims for foods to be evaluated and agreed by experts before they can be used.

The acceptance of the principle that health claims for foods should be allowed, is still relatively recent and legislation is developing differently in different countries. Nevertheless, the types of claims that are envisaged have been categorised by authorities and expert groups into (more or less) two classes:

- Health claims other than those referring to reduction of disease risk
- Claims referring to reduction of disease risk.

Some authorities (e.g. Codex Alimentarius) have subdivided the first class into two relating to “nutrient function claims” and “other function claims”, respectively. In the European Union, claims referring to children’s development and health are considered as a special subcategory of this class which have to undergo a more rigorous appraisal by the authorities. Essentially all of these claims describe the physiological role of a nutrient in growth, development and normal functions of the body, or they refer to specific beneficial effects of foods or food components beyond their generally accepted nutritional effects, other than the reduction of disease risk. For example, a claim might say that calcium aids in the development of strong bones and teeth and then draw attention to the calcium content of the food for which the claim is made. Or, it might say that consumption of a particular food helps to maintain a high state of mental alertness or physical performance.
Claims referring to reduction of disease risk are claims that consumption of a food or one of its components reduces a risk factor in the development of a human disease.

In some countries, such as the USA, an evaluation process for health claims is mandatory but, once approved, the claims can be used for all foods fulfilling the stipulated compositional criteria, that is, the claims are generic. In other countries, like Sweden, the Netherlands and the UK, voluntary codes of practice have been established by the food sector in co-operation with the authorities and provide procedures for evaluating claims. The evaluation process has not been part of the legislation and claims have been allowed, subject to the general food labelling rules. But, in enforcing the labelling rules, the authorities have taken into account whether claims have been evaluated and endorsed by suitably qualified experts. There is an expectation that health claims will undergo a process of substantiation before they appear on food labels. New legislation on nutrition and health claims has recently been adopted in the European Union and is currently in the process of being implemented. The rules apply in all Member States of the EU (replacing the codes of practice previously in place in Sweden, the Netherlands and the UK) and will, when they are fully implemented, require health claims to be substantiated by experts before they can be used.

Since food labelling laws, in most countries where they exist, regard advertising and promotional information provided in relation to specific food products to be equivalent to labelling, claims made in these ways must comply with the same rules.

How are claims to be substantiated?

For a claim to be truthful, it must accurately reflect its underlying basis. Substantiation of the claim should be based on a systematic review of the evidence relevant to the claim and an assessment of whether the wording of the claim is fully consistent with scientific evidence.

Several guidelines have been developed, for example, those in the USA, Canada, Australia/New Zealand and the UK give detailed guidance on the nature of scientific evidence to be provided and suggest how it should be evaluated. In Europe, following the completion of the FUFOSE Concerted Action, the European Commission funded a second activity to explore how claims might be substantiated. The project “Process for the Assessment of Scientific Support for Claims on Foods” (PASSCLAIM) had as its main objective the production of a generic tool to assess the scientific support for health-related claims for foods and food components. Its starting point was to examine the feasibility of the model developed by FUFOSE in which the consumption of functional food components is linked to health outcomes through the measurement of markers of target function or intermediate endpoints.

PASSCLAIM started by examining the available scientific data in seven different areas of physiological function, describing the scientific requirements for the quality of data to support claims that might be made and assessing the availability of markers to provide substantiation of these claims. From a broad-based analysis of the strengths and weaknesses of available methodologies for the assessment of health effects in different physiological areas, some general principles and criteria for the requirements for data provided as scientific evidence in support of claims were identified. The general principles (Box 4) provide a context in which the criteria (Box 5) should operate.
In summary, the criteria:

- Emphasise the need for direct evidence of benefit to humans in circumstances consistent with the likely use of the food
- Recognise the usefulness of markers of intermediate effects when ideal endpoints are not accessible to measurement
- Stress the importance of using only those markers that are of proven validity
- Highlight the necessity of ensuring that the magnitude and character of effects on which claims are based are statistically and biologically meaningful.

PASSCLAIM noted that the quality of evidence needed to support all health claims is similar. However, the type of data might vary. Claims relating to the conventional roles of nutrients in health might draw for substantiation on the generally accepted base of scientific knowledge while other (enhanced) function claims, being initially more specific, are likely to require specific scientific studies for their support. Disease risk reduction claims are likely to draw on support from across the broad spectrum of scientific data and rely mainly on studies showing reductions in disease-risk factors, i.e. by measurement of markers of intermediate endpoints (Figure 3).
The availability of a clear framework for conducting the assessment of scientific support for claims on foods benefits all stakeholders. Consumers have an assurance that claims have been validated and that all claims are assessed according to the same criteria. Food manufacturers and retailers who wish to make claims will know what evidence they must provide to substantiate them. Regulators are provided with a clear understanding of the limits of the validity of any particular claim.
**Informing other stakeholders – the broader picture**

Claims made on food labels, and the associated advertising and promotional literature for specific food products, provide the most direct way of communicating the benefits of functional foods to consumers. Incorporation of the concept of food functionality into awareness about nutrition through general education will ensure that consumers are equipped to understand the messages conveyed by claims, both so that they are not mislead and also so that they can take full advantages of the benefits on offer.

However, consumers are not the only stakeholders where diet and health are concerned. A growing body of scientific evidence points to the fact that functional foods have the potential to contribute positively to long-term health and well-being and disease risk reduction. Those potential benefits can best be delivered if all stakeholders (commerce, industry, agriculturists, educators, government and consumers) are sufficiently well-informed to motivate the introduction of functional food products into the marketplace. Food manufacturers, retailers, primary food producers, caterers, health care workers and governments all have roles to play and benefits to gain in ensuring that functional food science becomes part of general knowledge concerning nutrition, in the same way that knowledge about the role of vitamins and minerals in basic nutrition has become part of general knowledge in the past.

**FUTURE PERSPECTIVES**

Functional food science is still at an early stage in its development. As knowledge about the functional effects of foods increases and the functionality of particular foods and food components is more extensively recognised, technology will have a continuing role to play in making those foods and food components more widely available and accessible. Basic education in nutrition will also have a continuing role to play in ensuring that the benefits of functional foods are understood by all stakeholders in order to ensure that the benefits are enjoyed to the full. These aspects of future development are a continuation of activities already underway.

**The role of “omics” in the future development of functional foods**

Rather more exciting for the future of functional foods is the potential for the use of knowledge being gained in the fields of genomics, proteomics and metabolomics.

Genetic variation between populations and between individuals has long been recognised as a source of the variation that is evident in the outward appearance of individuals and in many aspects of their susceptibility to disease. There are well-established genetic links to conditions such as haemophilia, sickle cell anaemia and familial hypercholesterolaemia. There is also evidence that obesity is influenced by genetic factors. There is growing evidence that genetic factors influence the relationship between diet and the protective and risk factors for disease, and the ways in which different protective and risk factors can lead to the actual incidence of disease.
Until now, study of these interactions has been hampered by lack of a complete knowledge of the way an individual’s genetic makeup determines their physical and physiological profiles. This is, in part, because of the large number of genes involved; it has been estimated that the number of human genes must be counted in the tens of thousands. However, recent technologies provide the possibility of measuring large numbers of biological datum points simultaneously. It is now possible to visualise differences between the genetic profiles of individuals at the molecular level and to begin to understand how they relate to differences between individuals’ responses to physiological factors at the level of the whole organism. Similar techniques can be applied to gain an understanding of the way differences between other aspects of an individual’s molecular biology affect their response to physiological factors. These techniques are known collectively as “omics”. The study of the total genetic makeup (the genome) is known as genomics, and the study of the total metabolic profile (the metabolome) is known as metabolomics. Transcriptomics and proteomics are the terms that describe the study of the total gene expression and the total protein complement of an organism, respectively.

A greater understanding of the relationships between physiological responses at the level of the individual and their underlying bases at the molecular level has the potential to lead to the development of new markers of intermediate endpoints of relevance for improved health and reduced risk of disease. The accessibility of such markers to measurement by the application of “omics”-based methods may provide additional means to study the influence of dietary factors on human health and disease, leading to the identification of new routes to food functionality. The availability of markers responsive to short-term interventions and accessible to rapid, non-invasive measurement holds the promise of providing greater means to substantiate health claims, as well as to identify groups of individuals who might respond well or not so well to dietary interventions.

As greater insight into the basis for the variation between individuals’ physiological responses is gained from the application of “omics”, it may be possible for individuals to know whether they are at risk from, say, heart disease and to choose foods and diets that have the functionality to suit their particular needs. A synergy between developments in functional food science and “omics” may, in the future, result in a situation where it is possible for individuals to make truly informed choices about which foods provide the best opportunities for health, well-being and reduced risk of disease.
**Glossary**

**Antioxidant**: Substance that can delay or prevent oxidation.

**Atherosclerosis**: A degenerative disease of arteries in which there is thickening of the arterial wall caused by an accumulation of material (as a “plaque”) beneath the inner lining, eventually restricting blood flow. The accumulating material characteristically contains cholesterol and macrophages, a type of white blood cell.

**Bioavailability**: The fractional amount of a nutrient or other bioactive substance that, after ingestion, becomes available for use in target tissues.

**Cholesterol**: Lipid (sterol) made in the body and present in the diet; a constituent of cell membranes, plasma lipoproteins and atherosclerotic plaques.

**Codex Alimentarius**: This literally means “Food Code”. An organisation that creates and compiles standards, codes of practice and recommendations. Membership is open to all countries associated with the Food and Agricultural Organization of the United Nations and with the World Health Organization. At present (2005 figures) Codex has 171 member countries representing 98% of the world’s population. Non-governmental organisations also have input into Codex. (http://www.codexalimentarius.net)

**Cognitive ability, performance or function**: Capacity to perceive, assimilate and react to information.

**Disease risk reduction / risk factor reduction**: The outcome of an intervention whereby the chances of developing a disease may be reduced. In practical terms, it is often not possible to establish directly that an intervention causes a reduction in the incidence of a disease itself. Instead, the likelihood of the success of an intervention may be assessed by measuring the reduction in a risk factor for the disease (see “risk factor”). However, several risk factors may contribute to the development of a disease and a reduction in a single risk factor on its own will not necessarily produce a beneficial effect.

**Glycaemic Index**: The incremental area under the blood glucose response curve of a 50 g digestible carbohydrate portion of a test food expressed as a percentage of the response to the same amount of digestible carbohydrate from a standard food (glucose or bread) taken by the same subject. This is a measure of the effect on blood glucose levels produced by consuming a given quantity of a test carbohydrate food, expressed relative to the effect on blood glucose levels produced by consuming the same amount of a reference carbohydrate food, usually glucose.

**High-density lipoproteins (HDL)**: Plasma lipoprotein with high density; contains relatively low amounts of cholesterol and other lipids and a high amount of proteins. It is regarded as beneficial because it transports cholesterol from atherosclerotic plaques to the liver, from where it is eliminated in the intestine (see also lipoproteins and low-density lipoproteins, LDL).

**Intervention study**: A study in which investigators intervene by allocating and establishing one or more treatments (“interventions”) to, or in, certain subjects.

**Lipoproteins**: Particles of protein and lipids that enable lipids to be transported by the blood in the plasma.

**Low-density lipoproteins (LDL) and very low-density lipoproteins (VLDL)**: Plasma lipoproteins containing high concentrations of lipids (which are low in density compared to that of water), including cholesterol. Increased concentration is a risk factor for coronary heart disease.
**Microflora**: A collective term for all the bacteria inhabiting a particular environment.

**Micronutrients**: Vitamins and minerals (as distinct from “macronutrients” – fats, carbohydrates and proteins).

**Mono-unsaturated fatty acid (MUFA)**: A fatty acid whose hydrocarbon chain contains a single carbon:carbon double bond. See also saturated fatty acid and polyunsaturated fatty acid.

**Platelets**: Cell fragments in blood involved in clotting.

**Polyunsaturated fatty acid (PUFA)**: A fatty acid whose hydrocarbon chain contains two or more carbon:carbon double bonds. See also saturated fatty acid and mono-unsaturated fatty acid.

**Prebiotic**: A non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or modifying the metabolic activity of one or a limited number of bacterial species already established in the colon that have the potential to improve host health.

**Probiotic**: A live microbial food ingredient that, when ingested in sufficient quantities, confers a health benefit on the consumer.

**Reactive oxygen species (ROS)**: Forms of oxygen that, because of their chemical structure, have enhanced chemical reactivity compared with the normal oxygen molecule. They are believed to be major contributors to ageing and to many of the diseases associated with ageing.

**Risk factor**: Something that increases the chances of developing a disease.

**Saturated fatty acid (SFA)**: A fatty acid whose hydrocarbon chain contains no carbon:carbon double bonds. See also mono-unsaturated fatty acid and polyunsaturated fatty acid.

**Substrate**: A substance upon which a specific enzyme or metabolic process exerts its effects, or which serves as an energy or nutrient source for micro-organisms.

**Synbiotic**: A mixture of probiotics and prebiotics that beneficially affects the host by favourably modifying the gut microflora and its metabolism.

**Target function**: A biological activity, ongoing in the body, that is a target for intervention and measurement with a view to the maintenance or improvement of health and well-being and/or reduction of risk of disease.

**Thrombosis**: Blockage of a blood vessel due to activation of the clotting process.

**Triacylglycerol (TAG)**: Glycerol esters of fatty acids; the form in which fat is stored in fatty tissue. Elevated levels in blood plasma in association with raised plasma cholesterol are associated with an increased risk of cardiovascular disease.
FURTHER READING AND REFERENCES


Other ILSI Europe Publications

Concise Monographs

- Alcohol – Health Issues Related to Alcohol Consumption
- A Simple Guide to Understanding and Applying the Hazard Analysis Critical Control Point Concept
- Calcium in Nutrition
- Carbohydrates: Nutritional and Health Aspects
- Caries Preventive Strategies
- Concepts of Functional Foods
- Dietary Fibre
- Food Allergy
- Food Biotechnology – An Introduction
- Genetic Modification Technology and Food – Consumer Health and Safety
- Healthy Lifestyles – Nutrition and Physical Activity
- Microwave Ovens
- Nutrition and Genetics – Mapping Individual Health
- Nutrition and Immunity in Man
- Nutritional and Health Aspects of Sugars – Evaluation of New Findings
- Nutritional Epidemiology, Possibilities and Limitations
- Oxidants, Antioxidants, and Disease Prevention
- Principles of Risk Assessment of Food and Drinking Water Related to Human Health
- The Acceptable Daily Intake – A Tool for Ensuring Food Safety
- Threshold of Toxicological Concern (TTC)
- Type 2 Diabetes – Prevention and Management
- Approaching to the Control of Enterohaemorrhagic Escherichia coli (EHEC)
- Assessing and Controlling Industrial Impacts on the Aquatic Environment with Reference to Food processing
- Assessing Health Risks from Environmental Exposure to Chemicals: The Example of Drinking Water
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- Exposure from Food Contact Materials
- Foodborne Protozoan Parasites
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- Food Safety Objectives – Role in Microbiological Food Safety Management
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- Nutrition in Children and Adolescents in Europe: What is the Scientific Basis?
- Overview of the Health Issues Related to Alcohol Consumption
- Overweight and Obesity in European Children and Adolescents: Causes and Consequences – Prevention and Treatment
- Packaging Materials: 1. Polyethylene Terephthalate (PET) for Food Packaging Applications
- Packaging Materials: 2. Polystyrene for Food Packaging Applications
- Packaging Materials: 3. Polypropylene as a Packaging Material for Foods and Beverages
- Packaging Materials: 4. Polyethylene for Food Packaging Applications
- Packaging Materials: 5. Polyvinyl Chloride (PVC) for Food Packaging Applications
- Packaging Materials: 6. Paper and Board for Food Packaging Applications
- Packaging Materials: 7. Metal Packaging for Foodstuffs
- Recontamination as a Source of Pathogens in Processed Foods – A Literature Review
- Recycling of Plastics for Food Contact Use
- Safety Assessment of Viable Genetically Modified Micro-organisms Used in Food
- Safety Considerations of DNA in Foods
- Salmonella Typhimurium definitive type (DT) 104: A multi-resistant Salmonella
- Significance of Excursions of Intake above the Acceptable Daily Intake (ADI)
- The Safety Assessment of Novel Foods and Concepts to Determine their Safety in use
- Threshold of Toxicological Concern for Chemical Substances Present in the Diet
- Transmissible Spongiform Encephalopathy as a Zoonotic Disease
- Trichothecenes with a Special Focus on DON
- Using Microbiological Risk Assessment (MRA) in Food Safety Management
- Validation and Verification of HACCP

Reports

- Addition of Nutrients to Food: Nutritional and Safety Considerations
- An Evaluation of the Budget Method for Screening Food Additive Intake
- Antioxidants: Scientific Basis, Regulatory Aspects and Industry Perspectives
- Applicability of the ADI to Infants and Children
- Approach to the Control of Enterohaemorrhagic Escherichia coli (EHEC)
- Assessing and Controlling Industrial Impacts on the Aquatic Environment with Reference to Food processing
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