

Functional Foods

Position and future perspectives

This study has been carried out under auspices of the National Council for Agricultural Research (NRLO) and the Council for Health Research (RGO) by:

Dr. S.P. Plaami, Wageningen University

Dr.ir. M. Dekker, Wageningen University

Prof.dr. W. van Dokkum

Dr. Th. Ockhuizen, The Dutch Dairy Foundation on Nutrition and Health

National Council for Agricultural Research

P.O. Box 20401

2500 EK The Hague

tel.: 0031 70 378 56 53

internet: <http://www.agro.nl/nrlo/>

Council for Health Research

P.O. Box 16052

2500 BB The Hague

tel.: 0031 70 340 75 21

ISBN: 90 - 5059 - 121 - 3

Parts of this report may be reproduced if their source is credited.

NRLO report no 2000/15, The Hague, February 2001

Preface

There is still much to be learnt about health promoting components in foods, especially in enriched functional foods. Some growers are developing crops with a higher content of components, the health effects of which still have to be demonstrated by nutritionists. Concern about possible mismatch between nutrition and health research and product development was the reason for the National Council for Agricultural Research (NRLO)* and the Council for Health Research for research and development (RGO) to submit a project proposal to the Consultative Committee of Sector Councils (COS) for funding by the Co-ordination Fund of the Sector Councils. The project objective was to develop a framework for an integrated approach of health, nutrition and food technology in developing products with health promoting effects.

The project was managed by Prof. Dr. W.M.F. Jongen (Wageningen UR, project leader), Prof. Dr. W.H.M. Saris (University Maastricht) and Prof. Dr. D. Kromhout (RIVM).

Throughout the project, the concepts were discussed in workshops with experts from industry, research organisations, government and societal organisations. The results of the discussions have been incorporated in the final report. The main conclusions concern the need for an integrated approach throughout the production chain because bioactive components present in the raw material may be influenced by the processing steps in different ways. There is also a need for pre-market modelling to assess accumulative and interactive effects of these and other components in the diet. Finally, the effects on consumer health need to be monitored in Post-Marketing Surveillance after market introduction of functional foods.

We are confident that this study will contribute to the further development of an extensive knowledge base and responsible evaluation of functional foods.

On behalf of the participating councils:

Dr. J.M.P. Papenhuijzen
National Council for Agricultural
Research (NRLO)

Dr. C.H. Langeveld
Council for Health Research
(RGO)

* Since 1 October 2000 Innovation Network Rural Areas and Agricultural Systems.

Contents

Preface	i
Executive Summary	1
1. Introduction	5
2. Project purpose and approach	7
3. Conceptual framework: integrating health, nutrition and food technology sciences	9
4. Nutraceuticals	13
5. Consumer and market needs	15
6. Requirements of functional foods	19
7. Expertise & skills: consequences	23
8. Efficacy of functional foods	31
9. Claims	33
10. Safety	37
11. Pre-Market Modelling	39
12. Product launch	43
13. Business evaluation	45
14. Post-Marketing surveillance/ post-launch monitoring (PLM)	47
15. Legal aspects and evaluation procedures	49
16. Recommendations	53
Acknowledgements	55

References	57
Appendices	
1. Short review of some specific classes of functional foods	
2. Specific safety questions for the classes of functional foods	63
3. Following conclusions	65
4. Research recommendation	69
5. List of participants	71
Glossary and abbreviations	75

Executive Summary

Various food components are being studied for their potential role in promoting health and preventing (chronic) diseases beyond the accepted nutritional concepts. The approach of recommending a well-balanced diet, for example to meet the requirements for macro- and micronutrients, is evolving towards the concept of optimal intakes for optimising health and improving quality of life. There is great interest from food companies in commercialising this development by bringing to the market functional foods with health claims. Substantiation of these claims is not always a well formalised process and often leads to debate by the different players: food industry, experts in various scientific disciplines, consumer groups and governmental organisations. This report endeavours to clarify the different aspects of functional foods in an integrated approach to their development. The various viewpoints on aspects such as food technology, nutrition and health, legal aspects of health claims and the consumer perspective have been discussed by experts in these areas in a series of workshops. The desired developments and gaps in knowledge and in our current approach to functional foods have been identified.

Where there are indications that certain compounds in our food can have beneficial effects on human health or well being, parallel development must be initiated in nutrition and health sciences and in food technology. The only efficient way of developing effective functional foods is in an integrated approach that takes account of all aspects in the food production chain - from primary production of raw materials with appropriate levels of the bioactive compounds to the effects of these compounds on consumer health. Based on the discussions, literature review and interview with various experts, the main recommendations of this study are:

1. In developing safe and effective functional foods, pre-market modelling and post-marketing surveillance are essential tools because of nutritional requirements based on the total dietary intake that may include several foods and nutraceuticals (food supplements, herbs and herb medicines) with interacting active ingredients. For these purposes, it is essential to include intake of nutraceuticals as a separate category in databases of the national consumption surveys.
2. A reliable system for evaluating health claims and safety of new functional foods could be the establishment of independent national and/or EU food authorities. The various Codes of Conduct in the EU and Member States need to be harmonised. The requirements for the dossier for the approval of a product and its associated health claims should be established by a government agency and harmonised in the EU countries. This needs to be communicated effectively to companies interested in developing functional foods.

3. Development of effective functional foods requires appropriate knowledge management throughout the production chain of all disciplines involved including technology, nutrition, health and consumer behaviour. Long-term marketing success of functional foods depends on the food industry's ability to move to more high-tech and multi-disciplinary production systems.
4. In-depth understanding of consumer needs and purchasing behaviour with respect to diet and health is essential for the development and introduction of functional foods.
5. Current knowledge about health promoting bioactive compounds is limited to a few groups of compounds. It is reasonable to assume that many more compounds with, as yet unknown, but similar or even more pronounced effects on health are present in foods. Identification of such components is a research challenge.
6. A shift in nutritional concepts from preventing deficiencies to optimising individual intake levels of bioactive compounds is essential for effective positioning of functional foods.
7. Optimal intake and upper safe limit values have to be determined for functional bioactive components.
8. It is essential to establish reliable and efficient ways of communicating developments in functional foods to consumers. A valuable step is a logo on product package, which designates approval of the health claim by the recognised independent authority.
9. Because total dietary intake of bioactive components is not only restricted to functional foods, it is recommended that nutraceuticals (food supplements and herbal medicines) should be reviewed.

More detailed recommendations on specific research elements derived from individual workshops and literature are presented in Appendix 3 and 4.

Actions to be taken from the recommendations for The Netherlands:

1. A project on the pre-market modelling of functional foods is to be undertaken by Wageningen University and TNO and sponsored by the Innovation Network Rural Areas and Agricultural Systems.
2. The Innovation Network Rural Areas and Agricultural Systems and KLICT should take the initiative to implement recommendation 2: Knowledge management throughout the whole food production chain, including product development and technology.
3. The Ministry of Health (Health Council) should take the initiative to implement recommendation 6: Inclusion of nutraceuticals (supplements, herbal products and medicines) as a separate category in the national food consumption surveys.
4. The Health Council will take the initiative to implement recommendation 7: Implementation of a reliable system of evaluating health claims and safety of new

functional foods by an independent national and/or EU Food authorities. For this, the “Beraadsgroep voeding” could be widened to include experts throughout the food production chain in order to develop a more integrated approach.

5. The Innovation Network Rural Areas and Agricultural Systems and/or the RGO should take initiative to implement recommendation 9: Set up a committee to review the concepts of nutraceuticals including health, nutritional and technological aspects.

1. Introduction

The approach of recommending a well-balanced diet to meet intake requirements for macro- and micronutrients is evolving towards the concept of optimal intakes to optimise health and to improve the quality of life. This has already resulted in the use of fat and sugar replacers to decrease fat and carbohydrate intake thus reducing energy intake, and in the development of sport foods to improve physical performance. There has also been renewed interest in micronutrients such as those with antioxidant activity, with recommendations for intakes beyond the traditionally officially recommended dietary allowances. This idea is based partly on new insights into the function of vitamins, such as folic acid. As well as preventing certain forms of anaemia, folic acid is known to prevent neural tube defects. In addition, folic acid, vitamins B6 and B12 are assumed to play a role in decreasing homocysteine levels in blood, and if a causal link is established between homocysteine concentration and cardiovascular disease, increased intake of these vitamins may be recommended. Again, the role of plant sterols and stanols in decreasing serum cholesterol levels seems to be more efficacious than the classical ways of controlling serum cholesterol concentration by decreasing the intake of saturated and *trans* fatty acids and an increased consumption of mono- and polyunsaturated fatty acids.

These and other developments have led the food industry to introduce a number of products that are claimed to be beneficial for specific physiological functions, including physical and mental performance, or to have an added nutritional value. These products, which are known as functional foods may contain either bioactive constituents in a higher quantity than present in corresponding conventional foods (such as for antioxidant vitamins) or may have a reduced levels of undesirable components (such as saturated and *trans* fatty acids).

This project has been initiated because it is thought that rapid market developments in functional foods should be accompanied by commercial decisions based on an integrated approach, taking into account food technology, nutrition and health, legal aspects of health claims and consumer behaviour. This implies that functional foods should be developed in the context of a total diet aimed at optimising health.

2. Project purpose and approach

The purpose of this project is to identify:

1. Criteria to be met in approving health claims of functional foods;
2. Knowledge needed to predict bioavailability and bioactivity of functional components in a specific food matrix:
3. Ways of integrating a product approach with general dietary intake recommendations:
4. Gaps in knowledge and ways of dealing with specific aspects of functional foods.

The work scheme for this project is set out below.

- A literature review was carried out in order to present the latest developments in technology, nutrition and health aspects of functional foods.
- A work scheme was set up to include all area of knowledge required in the development of functional foods (see Chapter 3).
- A group of experts was identified and invited to attend a series of meetings and for individual consultation.
- A kick-off meeting was organised at which the group of experts in relevant areas determined the approach for the project.
- Expert workshops were organised on the technological aspects, on health and health claims and on the efficacy, effectiveness and safety aspects of functional foods.
- The findings of the literature review and the workshop discussions and interviews have been incorporated in this report.
- The project concluded with a workshop at which the main elements of the project were discussed and further input was obtained from presentations on the industrial, consumer, and legal aspects of functional foods.
- Results of this workshop have been incorporated in this report.

3. Conceptual framework: integrating health, nutrition and food technology sciences

The primary function of food in the human diet is to provide energy and nutrients - macronutrients (protein, fat, and carbohydrates) and micronutrients (minerals, vitamins and trace elements). Food also has a secondary function of giving sensory satisfaction in its flavour, taste, colour and texture. Recently, there has been renewed interest in a third function - the capacity of food to modulate physiological systems (immune, endocrine, nervous, circulatory and digestive) beyond the accepted nutritional effects.

Research has shown that a variety of food components currently classified as non-nutrients do have biological activity that can modulate physiological functions in the body. There are non-nutritive components such as dietary fibre and secondary plant metabolites in our food, which are present in mostly small quantities and have only limited caloric value. By modulating physiological functions, these food components can be responsible for the beneficial effects connected with certain foods and diets. Thus, from the point of view of preventing food spoilage, adding nutritional value and raising sensory quality, we are now moving towards a new generation of foods that have additional health promoting or protecting benefits.

Functional food is a new concept in nutrition that requires research on the physiological effects of non-nutritive compounds and of nutrient intake beyond levels that prevent deficiencies (1). An integrated approach that includes health science, nutritional science and food technology is needed in order to produce foods with measurable health benefits.

Food companies need to be able to quantify the health promoting potential of a product in order to provide consumers with reliable information. This requires knowledge about the occurrence (role in raw material, processing behaviour), bioavailability, effectiveness (mode of action, dietary recommendations) and efficiency (cost-benefit-ratio). Co-operation of professionals in nutritional and health sciences and food technology in all stages in the development of functional foods (Figure 1) is essential in order to obtain the data needed to substantiate health claims.

All disciplines involved in the development of functional foods are presented in the conceptual framework in Figure 1, which has also been used as the structure for this report.

Currently, there is no universally accepted definition of functional foods. A slight modification to the definition proposed by ILSI Europe (1) has been used as a working definition of functional foods in this report:

‘A food can be regarded as ‘functional’ if it has been demonstrated by sound scientific research 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. Functional foods must remain foods and they must demonstrate their effect in amounts that can normally be expected to be consumed in the diet: they are not pills or capsules, but part of a normal food pattern. A functional food can be a natural food, a food to which a component has been added, or a food from which a component has been removed by technological or biotechnological means. It can also be a food where the nature of one or more components has been modified, or a food in which the bioavailability of one or more components has been modified, or any combination of these possibilities. A functional food might be functional for all members of a population or for particular groups of the population, which might be defined, for example, by age or by genetic constitution’.

A review of various classes of functional foods is given in Appendix 1.

In developing functional foods, companies will need to establish a technology platform which integrates (Figure 1) technological know-how with knowledge of nutrition, health and legal aspects related to health claims. This platform should also map corresponding organisational and administrative changes necessary to respond to the demands raised from the shifts in business environment.

For a company, it is important to reduce the time lag between laboratory findings and implementation – to link technical capabilities with consumer demand. Managing technology often means strategic partnerships and consortia. When producing functional foods the producer must consider, in addition to the general issues in food production, also the added physiological function that the product should provide (the health claim). The health promoting qualities of a food product will need to be quantified and evidence provided of the validity of the claims as well as guarantees about the product’s safety. Thus co-operation of professionals from nutritional and health sciences and food technology is essential during the development process in substantiating the health-promoting qualities of products. This is often realised in strategic alliances between food ingredient producers, food manufacturers and scientific research organisations.

Companies developing functional foods will need to integrate know-how in food technology, with knowledge about nutrition, health, and legal aspects. Often, this can be achieved in co-operation and strategic alliances of food ingredient producers, food manufacturers and scientific research organisations.

An essential condition for success is appropriate knowledge management in a chain perspective. Food industries wanting to produce functional foods will need to extend their knowledge base and market approach.

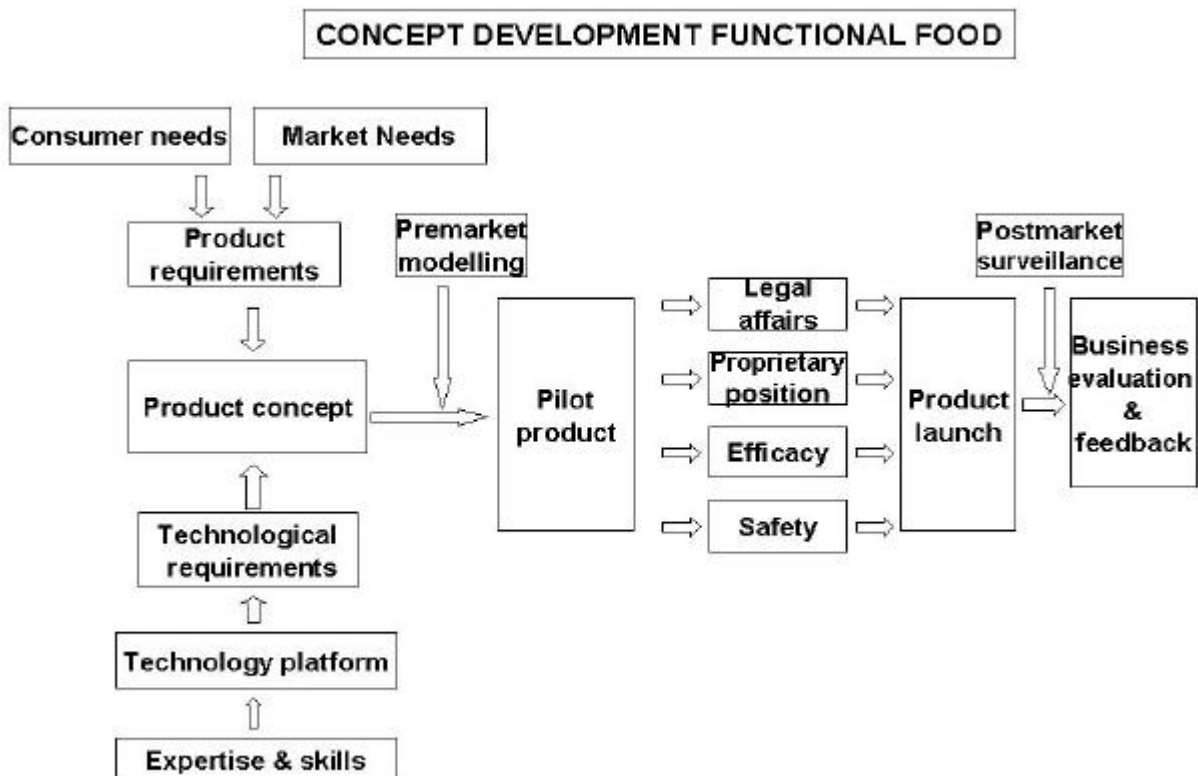


Figure 1. Conceptual framework for the development of functional foods.

4. Nutraceuticals

The ILSI definition of functional foods excludes supplements such as syrups, pills and capsules. Consumers, however, tend not to differentiate between functional foods and other products with health claims (nutraceuticals) such as supplements, herbal products including herbal medicines. There are regulations in the Netherlands and the European Union on vitamin and mineral supplements, and draft regulations have been prepared on safety aspects of herbal products. Other supplements and non-food, non-medicinal products are regulated only by food hygiene and safety regulations: producers are responsible for the safety of their products and cannot be permitted to make misleading claims about them.

These products have been not included in the definition of functional foods used in this report for practical reasons. The food matrix, which is an essential consideration in the development and production of functional foods, is not present in nutraceuticals. The considerations and recommendations in the report on safety, health claims, legal aspects, and on consumer and market demand are nevertheless also applicable to nutraceuticals.

In ensuring the safety and effectiveness of functional foods, both pre-market modelling and post-marketing surveillance are essential. Optimal intake levels and safety limits have to be based on the total dietary intake, which may include several foods and nutraceuticals that have interacting active ingredients. Thus, it is essential that intake of nutraceuticals is included as a separate category in the databases of national food consumption surveys.

It is recommended that a special committee be set up to review health, nutrition and technological aspects of nutraceuticals.

The ILSI definition of functional foods excludes food supplements such as syrups, pills and capsules. Consumers, however, tend not to differentiate between functional foods and other products with health claims (nutraceuticals) such as supplements, herbal products or herbal medicines. As nutritional requirements are based on the total dietary intake, which may include several foods and also nutraceuticals, intake of nutraceuticals (food supplements, herbs and herbal medicines) needs to be a separate category in national food consumption surveys. It is recommended that a special committee be set up to review health, nutrition and technology aspects of nutraceuticals.

5. Consumer and market needs

Socio-demographic trends are reflected in food consumption patterns and trends such as demand for convenience foods, smaller portions, variation, fun foods, travel foods and exotic foods and increased nutritional value and functionality (see Table 1).

Table 1. Impact of current socio-demographic trends on food consumption patterns in European countries (modified from 2)

Socio-demographic trends	Impact on food consumption
Formation of stable population size	Stable market size, increased competition, formation of niche markets
Ageing population	Demand for increased nutritional value and smaller portions, traditional taste
Greater ethnic mix in the population	Demand for exotic foods
Smaller households	Individual and smaller portions
Increased welfare	Added value foods
Increased education	Demand for increased nutritional value and "functionality", slow food, high quality level
Dual careers	Demand or convenience food
Individualisation variation	Smaller portion sizes, exotic food
Increased leisure time (many people in a work and spend cycle - busy week with free time at weekends and holidays)	Demand for fun foods
Increased mobility	Use of travel food and exotic food

By definition, a functional food is not a supplement; it is a food. As well as offering health benefits, a functional food must also taste good, be available at an acceptable price/value ratio and be considered safe. Functional foods need to be convenient and fit the image of targeted consumer group, such as offer variety, or have a 'natural' image, or be produced in an animal-friendly way (2).

A pan EU survey of consumer attitudes to food, nutrition and health found the main barriers to healthy eating were not lack of knowledge about nutrition but rather that health foods have the image of not tasting good and not being convenient to prepare (3). Taste was found to be more important than functionality in the acceptance of the functional foods (4). Alternative sources of the same functional component are needed to meet different food preferences and life styles and to prevent a product becoming uninteresting.

Consumers do not necessarily view functional foods as niche products, but rather as a natural evolution of conventional foods they have always eaten. They expect foods with health benefits to be available on regular supermarket shelves rather than in special aisles or in special shops. (5). It would be most convenient if a functional food could replace a food they eat regularly, such as a sandwich spread, breakfast cereal, cheese or drink. Furthermore, for the consumers it is easier to understand a health claim that is coupled to a brand, such as Benecol and Becel Pro-active and lowering cholesterol. This is also an advantage to the producer especially if the brand is successful.

Functional foods should not be developed for sale to a restricted target group. The best results are achieved when food products offering a health benefit (functional foods) are sold to the whole population, although individuals may not benefit equally.

If consumers are to buy functional foods and be willing to pay for the added value, they must be aware of the benefits. The sources of information about foods and their health benefits considered by consumers to be most objective are health care professionals, the media, and the government (6). There is a preference for packaging that communicates the health benefit of the functional component rather than information about the component itself (6). Furthermore, consumers associate a product with a content claim, such as contains dietary fibre, with a corresponding product-specific health claim - this product helps against constipation. Thus even if scientifically validated, content claims can be misleading for the consumer. Consumers want and expect better legislation and enforcement of the current legislation (7).

In general, familiar products and functional ingredients are found to be more credible and the natural source of the active component is highly preferred (8,9). In the USA, consumers show a mature understanding of the health benefits of vitamin C, vitamin A and calcium but are only beginning to become aware of the benefits of isoflavones, omega-3 fatty acids, probiotics or soy protein. There is still little consumer awareness of the benefits of vitamin E, folic acid, low fat and the importance of eating fruits and vegetables (10). In Denmark, Finland and the USA, on average only 8% of consumers knew about oligosaccharides and 31% about omega-3 fatty acids (9).

Consumers of functional foods believe that these foods can contribute to their own short-term and future health. In general, women are more likely than men to believe in the health benefits of foods. There is also a very strong positive relationship between income and education, and belief in functional foods. The belief is significantly higher among people aged 35 to 64 than among younger and older age groups (8). Younger consumers are less concerned about long-term benefits of functional foods, such as cancer prevention. They are more interested, for example in short-term energy boosts from sport bars, while older consumers are very interested in eating foods for long-term health benefits (10,11).

Consumers believe functional foods can offer health benefits for special diseases or undesirable conditions such as cardiovascular diseases, hypercholesterolaemia, overweight, colon cancer, osteoporosis, breast cancer, Alzheimer's disease and prostate cancer (8). There is also high consumer demand for mood-foods giving 'energy' or stimulating relaxation.

Consumers want functional foods that have health benefits but these foods must also taste good and be quick and easy to prepare. Functional foods are considered to be a natural evolution of conventional products and should thus be available on regular supermarket shelves.

Consumers believe that functional foods can contribute to their short-term and future health and are more likely to take notice of packaging that communicates the health benefit of the functional component rather than information about the component itself.

Consumers tend to associate a content claim with a corresponding product-specific health claim, and thus in spite of any scientific validity, content claims can mislead consumers.

Consumers want and expect better legislation on health claims and enforcement of the current legislation.

6. Requirements of functional foods

Consumer demands translate into requirements for food products as shown in Table 2.

Table 2. Consumer demands and requirements of functional foods

Consumer demands	Product requirement
Health benefit	Produces the health effect claimed and this is effectively communicated to consumers
Safe food	Fulfil hygiene and nutritional safety standards demanded for a functional food
Minimally processed }	Convenient to prepare
Quick and easy to prepare }	
Right package size }	
Tastes good }	Tastes good
Offers variety }	
Acceptable price/value ratio	Acceptable price/value ratio
Specific requirement }	Meets the attitude demands of the targeted consumer group
Animal friendly; 'natural'; snack food; }	
ethnic food; vegetarian; take-away food; }	
offers variety }	
Clearly defined target group }	Clear information on package and accompanying material about the product and how to use it
Who should eat the food }	
How often }	
How much }	

Other essential issues to be considered in the production of functional foods are product safety and the validity of the health claim. Nutritional safety of functional foods is linked to dietary behaviour. The risk attached to modifying certain dietary behaviour must be estimated by means of pre-market modelling (see Chapter 12). It is important to demonstrate a reasonable safety margin for the recommended intake levels and to specify the possible interactions with other constituents of the food or with medications,

taking into account that other products with ingredients that have the same or similar effect may lead to accumulative effects. Complementary to pre-marketing modelling is post-marketing surveillance (PMS; see Chapter 15) and requires a larger number of consumers for a longer exposure period under real life conditions.

Two aspects that must be checked with regard to the validity of health claims are efficacy and effectiveness. Efficacy measures the desired effect of a product under ideal conditions and answers the question: can the product produce the effect claimed? Effectiveness measures the effect of a product on the population at large under average conditions. For example, although a macronutrient replacer may have a lower energy value, it may not necessarily reduce the total dietary energy intake.

Quality assurance or the capability to ensure quality consistency is part of the safety, efficacy and effectiveness of functional foods. It concerns the ability to identify, measure and maintain a consistent level of the bioactive substance or an appropriate indicator compound in the product that ensures efficacy without jeopardising product safety. In some cases, there is no specific compound responsible for the effect, such as in slimming products. Quality assurance must then ensure the existence of the mechanism responsible for the claimed effect. It also encompasses the ability to demonstrate the reliability of the tests performed.

There are four elements of quality assurance in the development and production of functional foods:

1. Good manufacturing practices (GMPs)
2. Good laboratory practices (GLPs)
3. Good practices concerning the collection and analysis of human data – clinical and /or epidemiological practices (GCPs/GEPs)
4. Documentation

National or international guidelines for a commodity or food category, if established, should be followed.

As an example of the steps producers must consider in developing a functional food with ω -3-fatty acids are presented in Table 3.

Table 3. Steps and considerations in developing ω -3 long-chain PUFA products (modified from 13.)

<p>Step 1. Product concept and positioning determination</p> <p>Enrichment of an existing product line or the development of a completely new product Target population – narrow medical condition or more mainstream applicability Regulatory positioning Labelling (such as structure-function claim)</p> <p>Step 2. Product formulation and development</p> <p>Long-chain PUFA source/supplier and form (for example, fish oil, fermentation sources, oil/microencapsulated) Quantity added to provide an effect and be safe, pre market modelling (see Chapter 10) Additional ingredients (for example, antioxidants, flavour maskers/modifiers, texturing agents) Point of addition during processing Sensory analysis</p> <p>Step 3. Process optimisation and minimisation of long-chain PUFA oxidation</p> <p>Step 4. Studies providing evidence of effectiveness and safety</p> <p>Product specific human studies for efficacy, pre-market study and the plan for post-market surveillance studies</p>
--

Consumer demands of functional foods include good taste, scientific evidence for the health claim, safe, convenient, available at an acceptable price/value ratio, fit to the attitude demands of the targeted consumer. The health claim must be effectively communicated to consumers.

Producers of functional foods must consider (1) how to design the health benefit into the product, (2) identify the target population, (3) the regulatory positioning of the product as a functional food or as a supplement, (4) the package labelling (5) the studies needed to provide evidence of product efficacy and safety.

7. Expertise & skills: consequences

Food companies tend to use two strategies in selecting a market for functional foods (14). One approach is market opportunity-driven. Companies scan the literature, listen to consumers and health professionals. They recognise an opportunity to add value to their business by targeting a public health issue or they target fulfilling a consumer need (for example, by modifying an existing breakfast cereal product to substantiate a health claim about obesity, osteoporosis or constipation). The other approach is value-added driven. Companies research and improve their products, and then seek market segments that will benefit from the new attributes (for example, diabetics targeted for glucose absorption reducing breakfast cereals).

The implementation strategies in order of increasing risk are adding health benefits to existing products; adding new products with health benefits to an existing product line (line extension); creating new brands and setting up a new venture or company, for example, to produce bioactive ingredients (10).

Four types of technological skills used in the implementation process (15):

- Eliminating a component that has an adverse physiological effect, such as an allergenic, toxic or mutagenic compound.
- Increasing the level of a component that has a beneficial effect.
- Adding a particular ingredient seen as advantageous.
- Partially replacing a negative component with a positive entity in a processed food

These skills in the forms of present technologies are used in development of new functional foods.

Linnemann et al. (16) presented a model to translate consumer perception and food preferences to technological developments and priorities for the future. This model has been modified and used to identify technology and research needs in functional food science in Figure 2.

Technological skills together with the producer's experience determine which field, raw materials/primary products, refined products, ingredients or processed foods of functional food market the company may enter. The products from all these categories can, in addition of serving as raw materials in the production chain, also be ready functional foods or ingredients for the consumer.

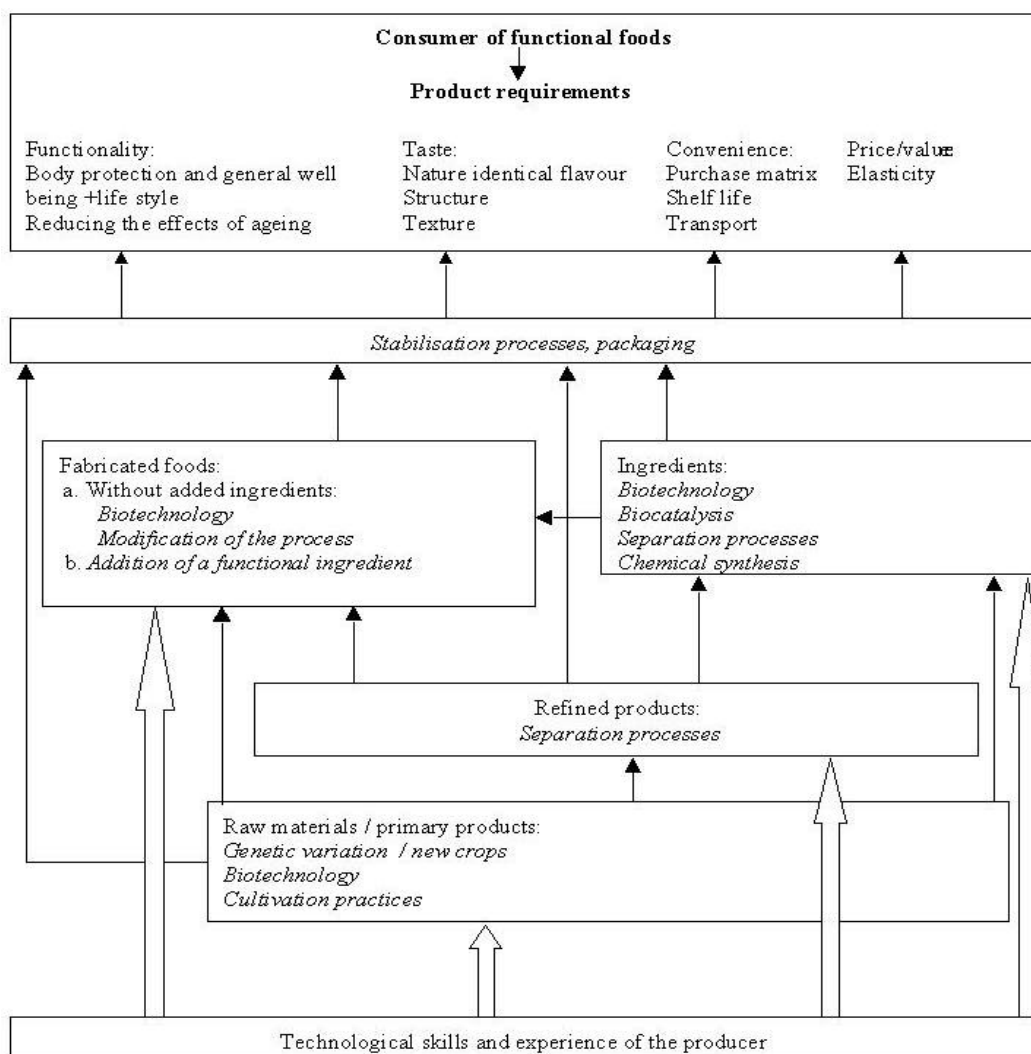


Figure 2. The translation of consumer's requirements for functional foods to the corresponding technologies

Raw materials/primary products:

The range of raw materials for functional foods can be extended by improved utilisation of the existing genetic variation.. This includes under-utilised and unconventional plants and selected varieties of now common crops containing known and also as yet unknown functional ingredients. Introducing genetic changes in common crops is another way to extend the range of raw materials.

Application of novel non-thermal stabilisation techniques may enable new raw materials to be used in producing functional foods, for example, use of electric pulse techniques to increase the bio-availability of minerals in fibre rich materials (17). The content of functional ingredients in raw materials and primary products can be influenced by agricultural practices (cultivation practices and animal feeding, for example, production of ω -3-fatty acid-enriched eggs.

Genetic modification can be an effective tool at various stages in the production of functional foods. However, there has been very little consumer acceptance for such

practices and the relationship between information provided and subsequent consumer behaviour is complex (18).

Novel foods with direct and tangible consumer benefits are more acceptable than those that benefit the food industry only. Consumer acceptance will increase with need and the advantages associated particularly with human health, environmental advantages, or animal welfare. Consumers accept drugs produced by genetically modified organisms (GMOs).

Consumers in Europe perceived the first genetically modified foods available as being beneficial to the food industry rather than to the consumer. The public is more likely to accept information about genetic modification from the European Commission and consumer organisations. These organisations are considered to be more objective because they provide information in the public's interest rather than to influence consumer attitudes and acceptance. Consumers need information about genetically modified foods in order to make informed choices about consuming them.

GMOs that offer specific personal benefit (such as GMO drugs) are readily accepted. Preference for such GMOs appears to be increasing where the information source is perceived to be objective and the information product-specific. Where consumers assume the information source is self-interest or partly so, the information provided to consumers should be balanced and general in content.

The acceptance of GMO-products appears to be increasing when the information source is perceived to be objective and the information is product specific. Thus an industry strategy of bombarding consumers with information about genetically modified foods is unlikely to raise consumer acceptance of such products. It may even have the reverse effect and generate negative attitudes. In disseminating information about specific products, food manufacturers might adopt labelling strategy, which alone is unlikely to result in attitude activation, or perhaps adopt a 'balanced information approach ' rather than a product-specific focus (18).

Refined products

Separation processes used in the production of refined products comprise four sequential steps (19):

1. Removal of insolubles, for example filtration or centrifugation.
2. Isolation of the fractions, for example by extraction or adsorption.
3. Purification of components or fractions, for example, molecular separation technologies, like supercritical extraction.
4. Refining a product, for example by removing water, solvent or traces of impurities by drying or crystallisation.

The cost of the final product is largely determined by the concentration in the initial raw material and isolation is the key step in controlling cost. The challenge is to develop

economically sound, large-scale separation processes to selectively purify product streams and to produce functional components.

Ingredients

Processes used to produce ingredients for functional foods include chemical synthesis, separation processes and biotechnology.

New functional ingredients could be established on the basis of a sound track record of safe use. In many cases, the compound groups are known, but more research is needed to justify the use in food production (glucosinolates, flavonoids, phytoestrogens). Food-processing waste streams may offer a rich source of desirable components for functional foods (phytoestrogens in soy bean processing).

Biotechnology has a long history in food industry. New opportunities for the production of ingredients are expected to come from technological developments in biocatalysis using enzymes and microorganisms. Enzymes are very specific in their activity, and thus offer an important advantage over many chemically induced conversions. They are used to modify biopolymers (dietary fibres) and in the synthesis of compounds such as aspartame, fats and amino acids.

Processed foods

Processed foods are created by the interplay of ingredients and processes such as crystallisation, emulsification, gelation, phase separation, extrusion, aggregation, baking, agglomeration and granule formation. These texturisation processes are essential elements of industrial processes and advanced process control is required.

Processed functional foods can be produced in one of two ways:

- Using technologies that
- produce functional ingredients for the product during manufacturing (biotechnology, for example, fermentation),
- Preserve, concentrate or increase the bioavailability of the functional ingredients already in the raw materials (for example, the effects of processing on bioavailability of lycopene, enzyme hydrolysis used to release the bioactive compound from cell matrix),
- Modify the product so that it becomes functional (for example fat technology)
- Adding a functional ingredient or adding ingredients that enhance the bioavailability of existing functional ingredient (adding vitamin C enhances the bioavailability of iron)

Production of processed functional foods requires knowledge of the processing behaviour of the bioactive ingredients. Certain processes are known to be efficient in

removing or degrading bioactive compounds almost entirely, such as oxidation of poly-unsaturated fatty acids or loss of flavonoids in juice processing. In specific situations, processing can also have advantageous effects on the level of bioactive compounds such as stress induced increase in glucosinolates, or bioavailability such as cooking of carotenoid rich plants or chopping folate rich vegetables. Adverse processing effects can sometimes be prevented by adding the bioactive compound in a later phase, or by use higher starting level or micro-encapsulated compound (see Table 3). In addition, processed 'ready-to-eat' foods (such as spreads, biscuits, breakfast cereals, cheeses and drinks), in which the uncontrollable household processing step can be avoided, are attractive food categories to be considered as carriers of functional ingredients. There is an urgent need for relevant markers of compound groups and monitoring methods for functional compounds (such as flavonoids and glucosinolates) and their functionality (target function). Dedicated, product-specific sensors for on-line measurements that can be applied in combination with computers also need to be developed.

Stabilisation and packaging

Stabilisation and packaging are important to secure food safety and physical stability of foods (preservation of sensory quality), and to protect the functionality of functional foods.

Stabilisation processes are generally based on inactivation (heating), inhibition (fermentation, drying, cooling/freezing), removal (membranes) and prevention (packaging). Novel non-thermal food processing technologies are becoming more importance (Figure 3). These processes aim at gentle, minimum, sometimes even, invisible processing in order to maintain the quality of raw materials, their physio-chemical properties and functionality as much as possible while assuring microbial safety, and ideally reducing environmental problems. Such processes may lead to metabolic responses of microbial populations. Sometimes stress responses in microbial populations to stabilisation processes can be used to increase the production of metabolite as functional ingredients (20).

A singular production process often comprises a number of stabilisation processes. The challenge is to develop technologies that not only improve product stability but also retain or improve the bioavailability of functional ingredients. The impact of non-thermal technologies needs to be explored further with regard to safety, quality functionality and regulatory issues. The use of non-thermal technologies may also enable novel raw materials to be used, resulting in unique functional foods.

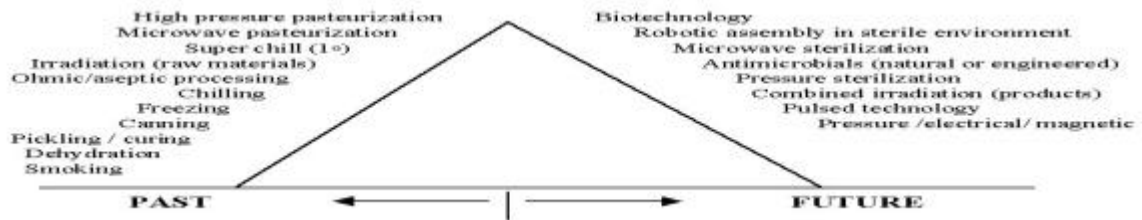


Figure 3. The technology hill of traditional and future preservation technologies (from 20).

Consumer preparation

The food industry cannot ignore the risk of incorrect storage and preparation of foods by consumers. The risks can be diminished by offering consumers proper quantities, using the appropriate packaging method and providing clear information. Correct kitchen preparation could sometimes be the step required to introduce or to increase the bioavailability of the functional ingredients. Studies on survival of functionality during storage and kitchen preparation and measurement of absorption and functioning, are essential to the life cycle analysis of functional foods.

Food production chain

The large number of variables in each step of the food production chain makes it impossible to quantify and optimise the dietary intake of bioactive compounds experimentally. Variation throughout the food production chain can be quantified scientifically using a predictive modelling concept of health aspects, which consists of a set of mathematical equations describing the fate of bioactive compounds in the food production chain (21).

In the model, essential parameters that determine the healthy-promoting qualities of the food need to be selected and the most critical sub-processes for each parameter during the whole process under study. These sub-processes are translated to mathematical equations, usually (partial) differential equations in combination with mass balances, describing what happens during processing.

This approach can be used to optimise the production chain for functional foods and to quantify intake level and potential health related benefits.

Food companies use market-opportunity driven and added-value driven approaches to select target groups for functional foods. The implementation strategies include adding health benefits to existing products; extending a

product line with products that offer health benefits; creating new brands; or by setting up a new venture or company for this purpose.

Efficient development of effective functional foods requires appropriate knowledge management throughout the food production chain and includes food technology, nutrition, health and consumer behaviour. Predictive modelling of health aspects with a set of mathematical equations describing the fate of bioactive compounds in the food production chain can be used to optimise the food production chain and to quantify intake and potential health related benefits.

8. Efficacy of functional foods

All functional foods launched on the market must have a scientific basis demonstrating how and to what extent target functions can be modulated and the relevance to well-being and health, including the possible risk reduction to certain (chronic) diseases. Scientific evidence should preferably be based on clinical and intervention trials in humans, ideally in combination with the results of in vitro studies, animal experiments and observational epidemiological studies showing a causal relationship between intake of a certain functional food (ingredient) and the envisaged improvement of a physiological function. The development of 'virtual cells', for example in testing compound effects on cell level by computer modelling will offer a valuable additional tool in evaluating efficacy. Sound scientific evidence is both objective and appropriate, but the same level of evidence for functional efficacy might not be available for each type of study. The example provided in the ILSI report concerns the effectiveness of certain antioxidants in reducing risk for different types of cancer. This is adequately supported by biological data (at molecular, sub-cellular and cellular level), but less well supported by epidemiological evidence and hardly at all by clinical intervention trials. For human studies, it is important to identify and validate markers that can predict potential benefits or risks to a target function in the body. These markers should be shown to relate to health outcomes such as chronic diseases or improved functions. The classification of markers shown in Figure 4 is derived from the ILSI report (1). The efficacy of functional foods in improving health and well-being can be evaluated according to the following sequence:

Scientific evidence needs to be provided that a (bio-active) component may modulate markers of health and/or well-being (for example, plant sterols may reduce serum cholesterol levels. It has been shown that there is a causal relationship between cholesterol and CHD).

Scientific evidence needs to be provided that these modulations are apparent in the matrix of a food (taking into account interactions, for example, during processing).

- Actual or envisaged consumption of the product within the food pattern of specific population groups needs to be indicated to provide evidence of how quantitatively a specific class of functional food could contribute to an envisaged improvement of health/physiological state or well-being, or at least an indication of the probability of the beneficial effect.

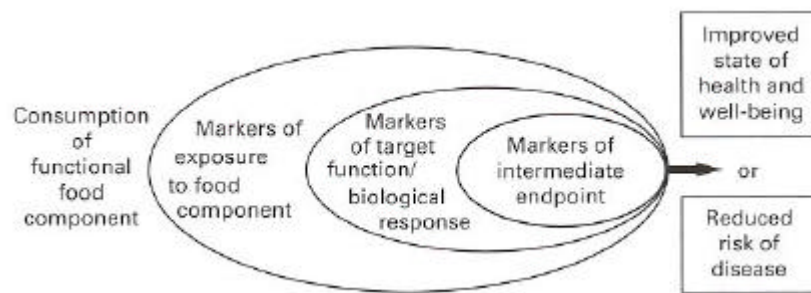


Figure 4. Classification of markers for the effects of functional foods (from ILSI report;1)

Functional foods should not be evaluated using pharmacological evaluation principles for which only randomised controlled trials are accepted as evidence. An independent authority should weigh the different types of evidence (in vitro studies, animal experiments, human trials, and epidemiological findings) in assessing efficacy of a functional food.

Additional evidence should not be required for product added to a line of functional products already on the market provided it can be shown that the active ingredient is present in the new food. This will prevent unnecessary studies. A case by case evaluation by an independent authority would therefore be sufficient.

Evaluation of the efficacy and effectiveness of functional foods and the demands for evidence could be in line with that in the Code of Conduct of the Dutch Voedingscentrum (22: see also the Chapter 11 Claims).

All functional foods to be launched on the market, require a scientific dossier which demonstrates how and to what extent target functions can be modulated and the relevance to well-being and health, including the possible risk reduction for certain chronic diseases. An independent authority should weigh the different types of evidence (in vitro studies, animal experiments, human trials, epidemiological findings) in assessing the efficacy of a functional food.

9. Claims

As consumer interest in the relation between nutrition and health increases, there is increasing need for valid and reliable information about the health benefits of both conventional and functional foods. Health professionals, educators, the media and the food industry all play an important role in this respect.

Information about potential health claims – made either as a direct statement on the food label or package or indirectly in supporting information – remain an area of intensive debate. It is essential that claims about functional foods are based on scientific information.

Any claim must be true and not misleading. The Codex Alimentarius (23) defines a claim as *'Any representation, which states, suggests or implies that a food has certain characteristics relating to its origin, nutritional properties, nature, production, processing, composition or any other quality'*.

The situation regarding health claims is more complex and different definitions are applied in different countries. The Food and Advisory Committee (UK) (24) has defined a health claim as *'any statement, suggestion or implication in food labelling and advertising that a food is in some way beneficial to health, and lying in the spectrum between, but not including, nutrient claims and medical claims'*. EU directive 2000/13/EG states: *'Labelling must not attribute to any foodstuff the property of preventing, treating or curing a human disease, or refer to such properties.'* In the USA, a health claim refers to any statement *'that expressly or by implication characterises the relationship of any substance to a disease or health-related condition'*. Thus in the UK, a health claim related to a disease would be considered to be a medical claim, whereas in the USA it would be regarded as a health claim.

Recently, Codex Alimentarius has defined four categories of claims:

- Claims related to dietary guidelines or healthy diets, such as *'diets low in saturated*
- Nutrient content claims, referring to the level of a nutrient contained in a food, such as *'high in calcium'* and *'low in fat'*.
- Comparative claims such as *Reduced; Less than; Fewer; Increased; More than.*
- Nutrient function claims, referring to the physiological role of a nutrient in relationship to growth, development and normal function of the body. Claims in this category are similar to structure/function claims in the USA. They make no reference whatsoever to a specific disease, pathological state or abnormal condition. Examples are: *'Calcium might help the development of strong bones and teeth'*, *'Contains folic acid which contributes to the normal development of the foetus'* or *'High in carbohydrate to*

These four categories of claims refer to known nutrients and their role in growth development and normal functions of the body and are based on established knowledge widely accepted within the scientific community. The ILSI report supports the development of two other types of claims, based on the scientific classification of markers for target functions. Claims must always be valid in the context of the whole diet and must relate to the amounts of foods normally consumed.

These additional claims are Type A claims (*Enhanced function*) and Type B claims (*Reduction of disease*).

Enhanced function claims (Type A) concern specific beneficial effects of food constituents on physiological or psychological functions or biological activities beyond their established role in growth, development and other normal functions of the body. This type of claim is similar to a structure/function claim in the USA. Examples are certain non-digestible oligosaccharides that may improve growth of specific bacterial flora in the gut, caffeine can improve cognitive performance and folate can help reduce plasma homocysteine levels.

Type B claims refer to reduction of disease risk, related to the consumption of a food or food component that might help reduce the risk of a specific disease or condition because of specific nutrients or non-nutrients contained in that food. These claims correspond to those referred to as health claims in the USA. Since 1998, the USA FDA has approved the following associations as a basis for disease reduction or health claims:

- Calcium and osteoporosis
- Sodium and hypertension
- Dietary fat and cancer
- Dietary saturated fat and cholesterol and risk of coronary heart diseases (CHD)
- Fibre containing grain products, fruit and vegetables and cancer
- Fibre containing grain products, fruit and vegetables and CHD
- Fruit and vegetables and cancer
- Folate and neural tube defects
- Dietary sugar and dental caries
- Soy protein and CHD
- Phytosterols and CHD
- ω -3 fatty acids and CHD with restricted scientific evidence

The ILSI report does not support a specific claim for improvement in health and well-being as these are sufficiently covered by the above two categories.

Currently, the first three Codex categories of claims are allowed in most countries, and to a much lesser extent, the fourth type of Codex claim and the Type A claims. Type B claims are almost universally disallowed. Food and compound-specific claims are easily

misleading, such as 'dietary fibre is good for colonic health', for which scientific evidence is not conclusive. The claim 'dietary fibre may prevent constipation' could be allowed as scientific evidence is abundantly available. However, to ensure that the claim is valid, only product-specific claims should be allowed. Scientific evidence should also include the various possible matrix effects, such as interactions between the bioactive compound and other components of the foods before ingestion (for example, interactions due to processing) and after ingestion (for example, effects on the bioavailability of the bioactive compound).

For a new product in a line extension of functional foods already on the market further studies in addition to the evidence that the active ingredient is present in the product are required only when specific matrix effects are envisaged. Omega-3 fatty acids for example, are easily available from a fat matrix, but if these acids are considered to be incorporated in bread, additional information should be provided on the effect of the bread matrix on the availability of omega-3 fatty acids. The Code of Conduct has an important role in providing the information and scientific support on efficacy (Gedragscode wetenschappelijke onderbouwing Gezondheidseffecten ten behoeve van Gezondheidsclaims voor eet- en drinkwaren 1998 of the Dutch 'Voedingscentrum':22; see also Chapter 16 Legal aspects).

If the efficacy of a functional food can be demonstrated by sound scientific evidence, prevention claims should be allowed. If the efficacy of a functional food can be proven at the end-point level, as is the case for several deficiency states (for example, increasing the intake of nicotinic acid cures pellagra), medical claims could also be allowed. Any form of a simple message, logo or identification number on the label of functional foods to identify approval of an 'enhanced function' claim (not so much of a 'reduction of disease risk' claim) could avoid misleading consumers, provided such a claim or logo is based on the opinion of an independent body, such as the Health Council.

Only product-specific claims should be allowed for functional foods. If the efficacy of a functional food can be demonstrated by sound scientific evidence, prevention claims should be allowed for functional foods
Medical claims should be permitted if the efficacy of a functional food can be proven scientifically at the end-point level.
A logo should be allowed on the package to indicate that the product has been evaluated and approved as a functional food.

10. Safety

All standards for assessing food risks require that all foods are safe and have no side-effects. A 100% safety guarantee cannot be given for any food - functional or conventional food. Foods must always be regarded as a source of potential toxic components. Food safety is thus a balanced evaluation of the risks and benefits. The concept of risk versus benefit cannot, however, be applied in the same ways as for drugs. Functional foods are so diverse that a checklist approach for safety evaluation is inappropriate. Rather, a case-by-case approach must be applied taking into account the composition of the functional ingredient, daily intake, role in the diet and the intended target group. This is the population group for which the functional food is supposed to have a higher benefit than for other groups. For example, the new plant-sterol margarines will be more beneficial to individuals with an elevated serum LDL-cholesterol level than those with a low serum LDL-cholesterol.

Acute reactions from the consumption of certain foods, such as allergy and food poisoning, are much easier to document than the chronic harmful effects resulting from nutritional imbalance. It is important to demonstrate that there is a reasonable safety margin for the recommended or envisaged intake and to specify the possible interactions with other nutrients or food components. Specific safety questions for the classes of functional foods described in Appendix 1 are given in Appendix 2.

For the safety evaluation of functional food ingredients, such as (phyto) chemicals, the daily intake of which is usually low, a traditional toxicology testing approach might be suitable. This is not necessarily the case for new functional food components, which might account for a relatively large percentage of the total food intake. The classic 'dose-effect relationship' might lead to considerations of physiological/nutritional disturbances that are irrelevant to standard safety assessment. Specific protocols and criteria for functional foods are needed and specific target groups of individuals should be identified who might present higher or lower susceptibilities to potential adverse effects. Moreover, functional foods might have positive effects in some target groups and negative effects in other groups. Pre-market modelling techniques to estimate the risk-benefit ratio of functional foods are presented in Chapter 12. The novel food regulation can be used as a guideline when considering pre-market modelling in the case of functional foods.

The long-term consequences of the use of functional foods can be monitored in a post marketing surveillance, which together with pre-market modelling, is an essential tool in safety evaluation of functional foods. For information on post-marketing surveillance, see Chapter 15

Food safety is always a balanced evaluation of risks and benefits. A case-by-case approach must be applied in evaluating functional foods, taking account of the composition of the functional ingredient, daily intake, role in the diet and the intended target group. This can be done using techniques in pre-market modelling and post marketing surveillance studies.

11. Pre-Market Modelling

The safety and efficacy of a new functional food should be evaluated in relation to the composition and expected variation in the diets of individuals. Possible interactions or cumulative intakes of active ingredients from different products should be taken into account in assessing efficacy and to prevent extreme intake levels and accumulation. Thus nutritional safety and efficacy of functional foods are linked to dietary behaviour, and pre-market modelling provides a framework to adequately estimate the risk/benefit ratio of modifying certain intake levels (12).

Functional foods are intended for a population generally in good health, and beneficial effects are only acceptable if they are obtained at a reasonable intake under normal use conditions. A reasonable intake must be effective and safe, and should not result in an adverse effect on the indicators studied in any population group. Pre-market modelling enables an estimate to be made of a desirable intake of the bioactive component in different food patterns and the corresponding effects. The risks of over-consumption by accumulation, possible adverse interactions or disturbances of the dietary equilibrium and the benefits with different levels of the compound in products can be evaluated. For example, what would be the effect of using functional foods containing extra calcium on the total mineral balance of consumers with different food patterns and calcium intakes? Pre-market modelling can be used to determine the safe and effective level of the bioavailability of the bioactive component in a specific functional food.

The study can be used as a basis for advice on whether the functional ingredient can be allowable in different food matrices. For example, is a cholesterol-lowering bioactive compound allowable in yoghurts, as well as in margarines or is there an unacceptable risk of over-dosage in groups who would consume both products? If permitted in both matrices, should the level be decreased in both product groups, and if so, would the product still be effective if groups only use one of the products?

Different modelling techniques can be used to answer questions of varying complexity (25) as presented in the examples below.

At a conceptual level, a model can be defined as a hypothesis about how a system works or responds to changes in inputs (26). The models discussed here are described in mathematical language, with equations and input variables, based on empirical or theoretical considerations. The purpose of a model is to represent a system of food consumption as accurately as is necessary for the intended application. For example, a model for a screening instrument may be very simple and less accurate provided it is conservative and on the safe side. Such models can help decision makers and risk managers to identify areas for regulation or further data collection. A research model to

enhance understanding of complex biological systems may be more extended and more complex itself.

In deterministic models, point estimates are used and no account is taken of variability and uncertainty in the input variables, Variability refers to real differences between and within populations, individuals and products. Uncertainty arises from lack of knowledge and is reduced when more data collected.

Probabilistic models use information about the distribution of the input variables. The uncertainty and variability in input variables is propagated through the model to obtain a quantitative insight into the range of possible model outcomes and the probability for each of these model outcomes. The most widely used probabilistic modelling technique is the Monte Carlo simulation technique (27).

There are several options for pre-market modelling, as shown in the examples below.

1. Simple simulation studies

Currently, the intake of a food component is calculated by multiplying the amount of food consumed by the concentration of the component in the food. In simple simulation studies, the concentration of an ingredient or component is changed and the calculation is repeated. An example is a simulation study of folic acid to investigate the prevalence of intakes below 400 µg or above 1000 µg per day in adult men and women after several theoretical enrichment schemes (28). A comparable study was carried out for iodine (29).

2. Scenario studies

In this type of study, more complex simulations are done, involving changes in more foods and in varying combinations. For example, data from the first Dutch National Food Consumption Survey (DNFCS) were used to investigate the effect of replacing fat rich products (partly or completely) by light products on the contribution of fat to total energy intake (30). This study also answered the question to what extent do fat-rich products need to be replaced by light products to obtain a specified average energy percentage of total fat.

3. Monte Carlo simulations

Monte Carlo simulation is a probabilistic method and the result of analysis is not a point estimate, but a distribution of possible model outcomes (31, 27). After constructing (conceptually and mathematically) a model, variables essential for the calculations (input variables) are determined. A distribution is attributed to the input variables based on experience and/or expert opinion, for example, it is known that the concentration of a residue in a food follows a log-normal distribution (after exclusion of observations below the detection level). From the distribution of each input variable, a value is sampled and the model calculations carried out. This results in one model outcome. This procedure is repeated say 1000 or 5000 times, to obtain a distribution of model outcomes.

4. Models to estimate usual intake from short- term measurements

With the help of modern techniques, habitual intake can be estimated from short-term measurements that normally do not give information on habitual intake distributions. The variation in short-term measurements consists of intra- and inter-individual variability. For estimation of habitual intake, only inter-individual variability is relevant. By unravelling the two sources of variability, a correction for intra-individual variability is possible, resulting in estimates of habitual intake (32,33,34). Later versions of this method can take account of heterogeneity in intra-individual variability and handle distributions that deviate strongly from the normal distribution (35,36).

The examples show that there is a range of modelling techniques to examine issues of varying complexity. In general, studies can be carried out using existing databases of food consumption surveys, such as the Dutch National Food Consumption Surveys in the Netherlands (37,38). In most cases, calculations can be done including and excluding food supplements, for the whole population, and for certain groups only. Since nutraceuticals (food supplements, herbs and herb medicines) supply many bioactive compounds for many consumers, it is essential to include intake as a separate category in databases of national consumption database surveys to enable more realistic modelling studies. As data collection on food consumption tends to be expensive, such modelling studies are generally highly cost-effective.

Pre-market modelling is the key element in linking the product-oriented approach used by companies to nutritional requirements at diet level, and linking nutritional safety of functional foods to dietary patterns. Pre-market modelling can estimate intake of the bioactive component in functional foods in different product categories and its effects at dietary level and *the benefits and risks at population level*. The potential risk of over-consumption by accumulation, adverse interactions or disturbances of the dietary equilibrium can be evaluated.

Since nutraceuticals (food supplements, herbal products and herbal medicines) are a supply many bioactive compounds, it is essential to include intake as a separate category in databases on national consumption database surveys to enable realistic modelling studies.

A range of modelling techniques is available to examine issues of varying complexity.

12. Product launch

During the development of a new product, the product and marketing program needs to be tested in realistic market settings. This involves launching the new product in regions of the country, carefully selected for a variety of geographical, marketing, and company reasons. These are large-scale commercial marketing experiments.

The main concerns in test marketing a new product are:

- Where and when to introduce a new product.
- How to introduce the product.

To gauge consumer reaction to the product, it is necessary to establish:

- How and when consumer uses the product.
- Whether consumers misuse the product.
- Whether the product message is being misinterpreted.
- Whether the instructions for preparation are clear.

In the case of functional foods, concerns about product safety must be evaluated, such as

- Can the product be consumed in excessive quantities by non-target populations.
- Does the new product disrupt the dietary balance – to the benefit of some foods and reduce consumption of others.
- Does the new product lead to negative perceptions about foods without health claims.
- Does the product induce short-term adverse effects, such as allergies or lead to new risk behaviour.

Data on the product effects on consumers need to be collected and analysed. Answers need to be obtained to questions related to the product itself, its protective package, the label, preparation or recipe instructions, pricing, and positioning of the product. The need for changes in the product, the process, or the package must be reviewed.

Test marketing gives management the information to make a final decision to go ahead with market launch of the product and thus with its commercialisation.

In addition to assessing potential sales, market testing of a functional food should be used to consider and test the product safety and the effectiveness of the product information. Are consumers misusing the product? Is the product message being misinterpreted? Are preparation instructions clear? Are there any other safety issues?

13. Business evaluation

At some stage during market testing there comes a time of reckoning. There are four measures to evaluate whether a product launch will be successful:

- Payback: when will the product make a profit for the company?
- Sales volume: when will sales volume goals, targeted percentage share of market or even significant market penetration be achieved?
- Consumer reaction: do consumers like the product, and how can the company capitalise on this?
- Tactics: "being there" is the strategy.

The reasons for the success or failure of test marketing must be examined. In the case of failure, what were the flawed systems or faulty information that led to incorrect decisions? In the case of success, what are the reasons for the product's success? Perhaps, these can be applied to another product launch in the future.

Measures used to assess the success or failure of a product launch are payback, sales volume, consumer reaction and tactics.

14. Post-Marketing surveillance/ post-launch monitoring (PLM)

Post Marketing Surveillance (PMS) encompasses the amount and pattern of consumption; the nature and degree of expected effects - beneficial and non-beneficial, and unexpected effects after a new food has been launched (as defined in Europe in EC Regulation 258/97/EC). Like pre-market modelling (PMM), PMS has the inherent limitations of any predictive testing, and it may be necessary to monitor aspects after market launch such as long-term consequences of consumption of functional foods. The term post launch monitoring (PLM) has been coined as a food-related term and to distinguish the procedure from post market surveillance (PMS) that is firmly associated with drugs.

Experience has been gained in the pharmaceutical industry with post marketing surveillance of drugs, which is an essential tool to identify adverse drug reactions. In the food sector, however, no post launch monitoring systems have been established and there is no relevant legal framework. A TNO-Unilever initiative has developed a concept of PMS for functional and/or novel foods (39). Furthermore, within the NWO (de Nederlandse Organisatie voor Wetenschappelijk Onderzoek) program Verantwoorde Voeding, a project was initiated by the UM and funded by RIVM to validate PMS. PMS was required in the USA as part of the admission procedure for the sweetener aspartame and the fat substitute Olestra. These examples illustrate that PMS can be performed passively and actively. In passive PMS, adverse health effects experienced by consumers can be reported via a toll-free telephone number. Complaints are registered and evaluated on the basis of a description of symptoms, products thought to be associated with symptoms, temporal association with consumption of the product, disappearance after cessation of consumption and recurrence of symptoms with repeated exposure, concurrent medications and search for medical attention because of the complaints. Active PMS can involve activities such as monitoring adoption and patterns of use of the new product in a representative sample of the population, evaluation of the effects of introduction of the product in a representative sample of the population, and assessment of long-term effects on certain parameters in a cohort of product users. The cases of aspartame and Olestra illustrate that post-launch monitoring can assess the incidence of unexpected and expected safety effects.

In the Netherlands, the admission procedure for phytosterols stressed the need to address the issue of PMS, and this is currently being done by the Standing Committee on Food. The following declaration was made by the Commission: "As a general orientation, the Commission considers that principles and guidelines concerning post-

market surveillance of foods should be addressed in the context of scientific co-operation (SCOOP), and only exceptionally through individual decisions concerning the authorisation of novel foods". Based on the examples of aspartame and Olestra and on the discussions at European and national level, it can be concluded that PMS is a potentially useful tool in the confirmation of the safety of functional and novel foods and should be scientifically validated.

The safety of functional foods with a history of safe use in Europe does not need to be re-assessed, according to the novel foods regulations. However, such considerations could be triggered if a functional claim is likely to lead to increased consumption beyond the level of the safe use history.

Possible elements for integration in a decision model for PMS are the safety and adverse effects of the functional food, its target group, consumption, efficacy and costs. Relevant factors in the operation of PMS are study design, recruitment of controls and users, and assessment of food consumption. In data collection, the use of permanent purchase panels might be helpful, and databases of producers may be helpful in the recruitment of users. It is worthwhile considering the feasibility of a standard approach to PMS.

Although the optimal study design will vary with the research questions and objectives, some elements could be standardised for reasons of reproducibility and efficiency.

Joint initiatives by the food industry, research institutes and regulatory authorities should help to shape the regulatory requirements for PMS, and to gain consensus on its rationale, what it can deliver and when it may be necessary. Furthermore, these initiatives determine whether it is possible to develop some general approaches, study designs and guidelines for conducting PMS.

Post-Marketing Surveillance (PMS) encompasses research on the amount and pattern of consumption of a functional food, the nature and extent of expected effects both beneficial and non-beneficial, and any unexpected effects after product launch.

PMS can be performed passively or actively. In passive PMS, adverse health effects experienced by consumers can be reported via a toll-free telephone number. Complaints are registered and evaluated. Active PMS can involve monitoring adoption and use patterns of the new product in a representative population sample, evaluation of the effects of a product launch in a representative population sample, and assessment of long-term effects on certain parameters in a cohort of product users.

15. Legal aspects and evaluation procedures

A brief summary is given of the formal legal aspects of market introduction of functional foods.

The EU Novel Foods Regulation (EU 258/97) was published in 1997. Although this regulation mainly concerns genetically modified organisms and products, some functional food ingredients fall into the category of novel foods. Moreover, this regulation focuses on food safety.

The EU Directive 2000/13/EG states that regarding health claims, labelling must not attribute to any food the property of preventing, treating or curing a human disease, or refer to such properties.

The official Dutch and EU policy on novel foods or functional foods is based on three criteria: the product must be safe; there should be freedom of choice; and information should not be misleading.

To launch a novel food in the European Union, a request should be forwarded to the authorities in one of the member states. In the Netherlands, the information (for which safety is the most important issue) is evaluated by a commission of the Health Council followed by a recommendation and report to the Minister. This report is sent to Brussels and to the authorities in the other member states, and may lead to approval for a product for market launch. In launching functional foods in the Netherlands, either the Code of Conduct of the Dutch Voedingcentrum (22) for the evaluation of health effects or 'Kode voor de Aanprijzing van Gezondheidsproducten' (KAG)(41) is applicable for addressing safety issues.

The Code of Conduct of Voedingcentrum is a voluntary agreement by industry, consumer organisations, nutrition educators, science and is supported by government. It has no official legal status. The Code sets out a procedure for evaluation of health claims and not medical claims, which are forbidden under Dutch Food Law. The scientific aspects of health claims are evaluated by a team of independent experts who examine the scientific evidence and the relevance of the functional food for target population groups. The envisaged health effects should not conflict with the general principles of current nutrition education for a healthy diet, as documented by the former Nutrition Council and the Health Council, and should be compatible with recommendations in international reports and documents.

A new functional food is evaluated at the request of its producer. The follow-up procedure is detailed in the Code of Conduct and comprises elements such as the formation of the team of experts, the time period for the evaluation, the level of

confidence regarding the information and the costs of the evaluation. The producer in a broad sense of a functional food is responsible for submitting information on the health effects to the team of experts and should also be responsible for pre-market modelling. The 'Voedingscentrum' is only responsible for the administration and technical support to the request; the team of experts is responsible for the scientific content of the evaluation. There is a high scientific threshold for the evaluation of the health effects of functional foods according to the procedure in Code of Conduct and very few requests have been made. Many more requests are received by the KAG for the evaluation of functional foods. The KAG procedure has a lower threshold for evaluation and mainly concerns nutraceuticals, the acceptability of proposed claims, and endeavours to relate a proposed claim with the product. The conclusions and recommendations have wide social acceptance.

The Code of Conduct of Voedingcentrum could be the basis for the evaluation of functional foods, in the Netherlands, and should be evaluated and modified to include all essential elements for the evaluation of functional foods - efficacy, effectiveness, safety and suggested claim. The novel food regulations could be used as a guideline for this purpose. Pre-market-modelling and post-market study should be included as essential parts of the dossier provided for the safety evaluation of functional foods.

The requirements for the dossier for approval of a product and its claim are currently being considered in the ILSI co-ordinated EU-project PassClaim.

A logo that is connected to a voluntary Code of Conduct would be of great help to consumers and of value to companies. This would avoid the undesirable situation in the USA with a health claim on one side of the package and on the other side the statement: 'the claim has not been proved'.

The company launching a functional food should be responsible for post-marketing surveillance as described in Chapter 15. The government should be responsible for post-marketing surveillance if this concerns evaluation of possible modifications to food patterns as a consequence of consuming functional foods or supplements containing the same functional compounds. The National Food Consumption Surveys carried out in various countries are potential tools for assessing the nutritional consequences of incorporating functional foods in the daily diet. It is necessary to include supplements in consumption surveys and via them in pre-market and post marketing surveillance studies, but it is difficult because of continuous and rapid changes in the constituents and quantities in them. This may, however, not be appropriate if functional foods are consumed by specific groups, such as patients.

Coherent legislation on functional foods is required throughout the European Union in the EU. A national EU food authority could be established in the Member States to review health claims. The work should start by harmonising existing national codes so that a product evaluation in one country could be accepted in other countries as well. This

would be an important step in eliminating trade barriers and enhancing opportunities for the industry as well.

Although the nature of the interaction between food components and gene expression is only partly understood, developments in this promising scientific area will have consequences for the role of functional foods in food intake patterns of individuals.

The Code of Conduct of the Voedingcentrum could be the basis for evaluation of functional foods in the Netherlands. The Code should be evaluated and modified to include all elements required in evaluating functional foods: efficacy, safety, proposed claims and effectiveness. The novel food regulation could be used as a guide for this modification.

Pre-market-modelling and post-market surveillance should be included in the dossier provided by producer for the independent expert evaluation of a food product for status as a functional food.

Coherent legislation on functional foods is required throughout the European Union. A national EU food authority could be established in the Member States to review health claims. The work should start by harmonising existing national codes so that a product evaluation in one country could be accepted in other countries as well.

It is necessary to include supplements in food consumption surveys and through these surveys in pre-market and post-market surveillance studies.

16. Recommendations

Based on the discussions, literature review and interviews with various experts, the main recommendations of this study are:

1. In developing safe and effective functional foods, pre-market modelling and post-marketing surveillance are essential tools because nutritional requirements based on the total dietary intake may include several foods and nutraceuticals (food supplements, herbs and herb medicines) with possible interacting active ingredients. For these purposes, it is essential to include intake of nutraceuticals as a separate category in databases of the national consumption surveys.
2. A reliable system of evaluating health claims and safety of new functional foods could be the establishment of independent national and/or EU food authorities. The various Codes of Conduct in the EU and Member States need to be harmonised. The requirements for the dossier for the approval of a product and associated health claims should be established by a government agency and harmonised in the EU countries. This needs to be communicated effectively to companies interested in developing functional foods.
3. Development of effective functional foods requires appropriate knowledge management throughout the production chain and must include all disciplines involved food technology, nutrition, health and consumer sciences. The long-term marketing success of functional foods depends on the food industry's ability to move to more high-tech and multi-disciplinary production systems.
4. In-depth understanding of consumer needs and purchasing behaviour with respect to diet and health is essential for the development and introduction of functional food concepts.
5. Current knowledge about health promoting bioactive compounds is limited to a few groups of compounds. It is reasonable to assume that many more compounds with, yet unknown, but similar or even more pronounced effects on health are present in foods. Identification of such components is a research challenge.
6. The development of new nutritional concepts that shift from preventing deficiencies to optimising individual intake levels of bioactive compounds is essential for effective positioning of functional foods.
7. Optimal intake and upper safe limit values have to be determined for functional bioactive components.
8. It is essential to establish reliable and efficient ways of communicating developments in functional foods to consumers. A valuable step is a logo on product package, which designates approval of the health claim by the recognised independent authority.

9. Because dietary intake of bioactive components is not only restricted to functional foods, it is recommended that also nutraceuticals (food supplements and herbal medicines) should be reviewed.

More detailed recommendations on specific research elements derived from individual workshops and literature are presented in Appendix 3 and 4.

Actions to be taken from the recommendations for The Netherlands:

1. A project on the pre-market modelling of functional foods is to be undertaken by Wageningen University and TNO and sponsored by the Innovation Network Rural Areas and Agricultural Systems.
2. The Innovation Network Rural Areas and Agricultural Systems and KLICT together should take the initiative to implement recommendation 2: Knowledge management throughout the whole food production chain, including product development and technology.
3. The Ministry of Health (Health Council) should take the initiative to implement recommendation 6: Inclusion of nutraceuticals (supplements, herbal products and medicines) as a separate category in the national food consumption surveys.
4. The Health Council will take the initiative to implement recommendation 7: Implementation of a reliable system of evaluating health claims and safety of new functional foods by independent national and/or EU Food authorities. For this, the “Beraadsgroep voeding” could be widened to include experts on the food production chain in order to develop a more integrated approach.
5. The Innovation Network Rural Areas and Agricultural Systems and/or the RGO should together take initiative to implement recommendation 9: Set up a committee to review the concepts of nutraceuticals including health, nutritional and technological aspects.

Acknowledgements

We would to thank all the participants of the workshops (Appendix 5) and T. Brussaard and M. Dusseldorp for their contributions to Chapters 12 and 15 respectively.

References

1. ILSI Europe. Scientific concepts of functional foods in Europe: Consensus Document. *British Journal of Nutrition* 81 (1999) Supplement 1, S1-S27.
2. Meulenberg MTG (1996) De levensmiddelenconsument van de toekomst. In *Markt en consument 2010*. NRLO-rapport nr. 96/4 november 1996.
3. Lappalainen R, Kearney J & Gibney M (1998) A pan EU survey of consumer attitudes to food, nutrition and health: an overview. *Food quality and preference* 9: 467-478.
4. Stubenitsky K, Aaron JI, Catt SL and Mela DJ (1999) Effect of information and extended use on the acceptance of reduced-fat products. *Food quality and preferences* 10: 367-376.
5. International food information council (1999)
<http://ificinfo.health.org/insight/fifall5.htm>
6. The National Institute of Nutrition (2000) Consumer Awareness of and Attitudes Toward Functional Foods. Highlights and Implications for Informing Consumers.
<http://www.agr.ca/food/markets/nutraceutu/cffr/ffnconen.html>
7. Hill and Knowlton (2000) 'Study on nutritional, health and ethical claims in the European Union' for the European Commission Directorate general for health and consumer protection.
http://europa.eu.int/comm/consumers/policy/developments/envi_clai/envi_clai03_en.pdf
8. Childs NM (1997) The functional food consumers: who are they and what do they want? Implications for product development and positioning. In *New technologies for Healthy Foods & nutraceuticals*, Manssur Yalpani (ed) ISBN 1-882360-10-9. Pp. 311-326.
9. Bech-Larsen T, Poulsen JB and Grunert G (1999) Acceptance of functional foods in Denmark, Finland and the US – a cross-cultural study of consumer values and preferences. <http://marketing.byu.edu/htmlpages/ccrs/proceedings99/bech-larsen.htm>
10. Witver RS (1999) Marketing bioactive ingredients in food products. *Food technology* 53, 50-53.
11. Schmidt DB, Morrow MM and White C (1998) Communicating the benefits of functional foods: Insights from consumer and health professional focus groups. In *Functional foods for disease prevention II. Medicinal plants and other foods*. Shibamoto T, Terao J, and Osawa T (eds) ACS Symposium series 702: 10-16.
12. FAO/WHO (Food and Agriculture Organization/World Health Organisation) Codex alimentarius commission (2000) Discussion paper on the scientific criteria for health related claims.

13. Garcia DJ (1998) Omega-3 long chain PUFA nutraceuticals. *Food technology* 52, no 6: 44-49.
14. Culhane C (1995) *Nutraceuticals / Functional Foods. An exploratory survey on Canada's potential.* International Food Focus Limited, Toronto, Ontario.
<http://www.agr.ca/misb/fb/food/markets/nutraceutu/nutra/enutra.html>
15. Gibson G and Fuller R (1998) The role of probiotics and prebiotics in the functional food concept. In 'Functional foods: the consumer, the product and the evidence. Sadler M and Saltmarsh M. (eds) Cambridge: Royal Society of Chemistry. Pp. 3-14.
16. Linnemann AR, Meerdink G, Meulenbergt MTG and Jongen WMF (1999) Consumer-oriented technology development. *Trends in Food Science & Technology* 9: 409-414.
17. Watzke HJ (1998) Impact of processing on bioavailability examples of minerals in foods. *Trends in food science & technology* 9: 320-327.
18. Frewer L, Scholderer J, Downs C and Bredahl L (2000) Communicating about the risks and benefits of genetically modified foods: effects of different information strategies. <http://www.mapp.hha.dk/WPpdf/wp71.pdf>
19. Singh PC and Singh RK (1996) Choosing an appropriate bioseparation technique. *Trends in food science and technology* 7: 49-58.
20. Knorr D (1998) Technology aspects related to microorganisms in functional foods. *Trends in food science and technology* 9: 295-306.
21. Dekker M, Verkerk R. and Jongen W.M.F. (2000) Predictive modelling of health aspects the food production chain, *Trends in Fd Sci and Techn.* 11(4/5), 174-181.
22. Voedingscentrum. 'Code of Conduct'. 'Gedragscode wetenschappelijke onderbouwing Gezondheidseffecten ten behoeve van Gezondheidsclaims voor eet- en drinkwaren 1998'. Den Haag, Voedingscentrum, 1998.
23. Codex Alimentarius, Second Edition. Codex General Guidelines on Claims. (CAC/GL 1-1979, rev. 1-1991), Geneva, WHO, 1991
24. Food Advisory Committee. Report on its review of food labelling and advertising. Report FDAC/REP/10, HMSO, London, 1991
25. Brussaard JH, Löwik MRH, Telman J. Modelling hulpmiddel bij blootstellingsschattingen. *VMT* 2000;(24):49-54
26. Cullen AC, Frey HC. Probabilistic techniques in exposure assessment. A handbook for dealing with variability and uncertainty in models and inputs. Plenum Press, New York and London, 1999
27. Vose D. Quantitative risk analysis: a guide to Monte Carlo simulation modelling. John Wiley and Sons, Chichester etc., 2000
28. Bausch-Goldbohm RA, Hulshof KFAM, Brants HAM, van den Berg H, Bouman M. De inneming van foliumzuur door verschillende bevolkingsgroepen in Nederland voor

- en na verrijking van bepaalde voedingsmiddelen. Voedselconsumptiepeiling 1992. TNO-rapport V95.184, Zeist, 1995.
29. Brussaard JH, Hulshof KFAM, Löwik MRH. Calculated iodine intake before and after simulated iodization (Dutch Nutrition Surveillance System). *Ann Nutr Metab* 1995;39:85-94
 30. Kistemaker C. Simulatiestudie aangaande de invloed op de vetconsumptie van vervanging van vetrijke producten door magere alternatieven, bij 22-49 jarige mannen. Voedselconsumptiepeiling 1987-1988. TNO-rapport V91.360, Zeist, 1991.
 31. EPA. Guiding principles for Monte Carlo analysis. Washington DC: US Environmental Protection Agency, 1997
 32. Beaton GH, Milner J, Corey P, McGuire V, Cousins M, Stewart E, deRamos M, Hewitt D, Grambsch PV, Kassim N, Little JA. Sources of variance in 24-hour dietary recall data: Implications for nutrition design and interpretation. *Am J Clin Nutr* 1979; 32:2546-2559
 33. Beaton GH, Burema J, Ritenbaugh C. Errors in the interpretation of dietary assessments. *Am J Clin Nutr* 1997;65(Suppl):1100S-1107S
 34. Slob W. Modeling long-term exposure of the whole population to chemicals in food. *Risk Analysis* 1993;13:525-530
 35. Nusser SM, Carriquiry AL, Dodd KW, Fuller WA. A semiparametric transformation approach to estimating usual daily intake distributions, *J Am Stat Ass* 1996;91(436):1440-1449
 36. Telman J. Modelling van dagelijkse inneming van voedselcomponenten. TNO-rapport FSP-RPT-990037, Delft, 1999
 37. Löwik MRH, Hulshof KFAM, van der Heijden LJM, Brussaard JH, Burema J, Kistemaker C, de Vries PJF. Changes in the diet in the Netherlands: 1987-88 to 1992. *Int J Food Sci Nutr* 1998;49(Supplement 1):S1-S64
 38. Anoniem. Zo eet Nederland 1998. Resultaten van de voedselconsumptiepeiling 1997-1998. Voedingscentrum, den Haag, 1998.
 39. M van Dusseldorp, D Welten, RA Bausch-Goldbohm. Post-launch monitoring of novel foods. TNO report V3136, dec 2000, Zeist, available on request
 40. The summary record of the 77th meeting of the Standing Committee on Foodstuffs (June 26, 2000, Brussels) http://europa.eu.int/comm/food/fs/rc/scfs/rap_01
 41. KAG ('Kode voor de Aanprijzing van Gezondheidsproducten'). Internet: www.koagkag.nl/leidraad/cagindex.

Appendix 1: Short review of some specific classes of functional foods (ingredients)

In order to specify which foods may fall under the definition of functional foods as described in the introduction, some examples of (classes of) functional foods are summarised.

Fat replacers

Fat replacers (or substitutes) may contribute to a reduction of fat intake. It will be essential that they have similar (sensoric) properties as those of conventional fat. Replacing fat by protein or carbohydrates on a weight for weight basis already results in a reduction of energy (and fat) intake. Modified fats or synthesised fats are generally not digested and absorbed, which means a considerable reduction of the fat intake or fat content when products with fat replacers are consumed. But there exists a risk for overestimation and overconsumption by the consumer. Scientific evidence for an improved food pattern and as a consequence a better nutritional status after consumption of products with fat substitutes is, however, weak. Moreover, most fat replacers do not contain vitamins.

Antioxidants

The (nutritional) interest in the significance of free radicals as a risk factor for the incidence of degenerative diseases is only acknowledged for one or two decades. One of the possibilities of 'fighting' free radicals is through the intake of antioxidants. The question is relevant whether an assumed optimal intake (whatever that may be) of antioxidants, either as an individual compounds (e.g. a specific vitamin) or as a combination can be realised through conventional foods or whether we need antioxidant-functional foods. 'New' bioactive compounds such as flavonoids are promising but the scientific evidence for a substantial improvement of the health status is only beginning to become available. Also for antioxidants there exists the risk of overestimation of the health promoting potential.

Probiotics and prebiotics

Already several decades the importance of dietary fibre for e.g. 'acknowledged, although results of recent studies show that no reduction of the risk for e.g. colon cancer is indicated when ample amounts of dietary fibre are consumed.

During the past couple of years a renewed interest has, however, risen for the various physiological and biochemical functions of the (human) colon. Beneficial bacteria (lactobacilli, bifidobacteria) may contribute to a healthier colon. To this end various functional foods (mostly in the fermented dairy product group) came on the market with specific bacteria that survive the stomach and small intestine to become available in the colon (probiotics). Also the 'functional foods for those bacteria' (prebiotics such as non-digestible oligosaccharides) were introduced, in some cases as a combination with probiotics ('synbiotics'). Apart from a direct effect on the physiology of the colon, it is assumed or postulated that pro- and prebiotics also may play a role in lipid metabolism and immune function, but the scientific evidence for a substantial effect is weak, if any.

Plant sterols and polyunsaturated fatty acids

Already for decades a low level of serumcholesterol for reducing the risk for coronary heart disease (CHD) is indicated. For many years the consumption of an ample amount of polyunsaturated fatty acids (through margarine, one of the oldest functional foods!) is recommended. The significance of very long-chain poly-unsaturated fatty acids present in fish for CHD prevention has also been acknowledged. Recently, the effects of plant sterols in reducing serum total and LDL cholesterol levels lead to the introduction of specific plant sterols containing margarines on the market. Although the evidence for the effect of plant sterols is substantial, an interesting discussion point remains whether these new types of margarine are the solution for arriving at a recommended low serum cholesterol level.

Minerals and trace elements

A few examples exist regarding enrichment of products with minerals or trace elements, but it is envisaged that in near future more functional foods will enter the market with extra amounts of metal elements. Milk with extra calcium (Calcium-plus milk) is already available for some time. The basic point, many times overlooked, is the aspect of bioavailability of minerals and trace elements, both from the product as such and from the mixed meal in which the enriched product is incorporated. Adding minerals and trace elements to foods does not necessarily mean that this improves health.

Sport foods and brain foods

Various foods are already on the market that claim an improvement of physical performance (e.g. with active components such as creatinine) or of mental performance (e.g. products with caffeine or tryptophane). Both categories of products may fall in the definition of functional foods as suggested by ILSI if their effects on improving health are shown.

Appendix 2: Specific safety questions for the classes of functional foods described in Appendix 1

- **Fat replacers:**

- * Is a risk for a reduced intake of fat-soluble vitamins realistic?
- * Is there a risk for an effect on bowel function by a too high intake of fat replacers?

- **Antioxidants :**

- * Is a risk for a too high intake of the various antioxidants through an envisaged consumption of a number of antioxidants-containing functional foods realistic?
- * What about interactions of the various antioxidants?

- **Probiotics and prebiotics**

- * Is there a risk for a too high intake of pro- and prebiotics resulting in disturbing of a 'normal' bowel function?

- **Plant sterols and fish fatty acids**

- * Do plant sterols (in margarines in a mixed diet) also inhibit the absorption of fat-soluble vitamins and other fat-soluble bioactive compounds?
- * Is the fact that fish fatty acids are easily oxidised a realistic health hazard?

- **Minerals and trace elements**

- * Is there a risk for an imbalance of the intake of the various minerals and trace elements when functional foods with extra amounts of these elements are consumed (interactions during digestion and absorption)?
- * If foods will be enriched with iron (in order to increase iron status) is it realistic to consider the possible increase of the formation of free radicals?

- **Sport foods and brain foods**

- * Does the intake of specific (active) components in these categories of functional foods bears the risk of adverse effects?

Appendix 3: Conclusions of the workshops

From the literature and as result of the discussions during the Technology Workshop the following conclusions were drawn:

- Technology should be able to produce functional foods with increased levels of bioactive ingredients even though the evidence for the functionality of these ingredients (non-nutrients) is not fully established in the health sciences. Physiological and health effects are separate issues, product development must go on already when there is some evidence of a physiological effect.
- Both biotechnology and processing can be used to enhance the level of bioactive compounds in a product. For consumer alternatives to GMO-enhanced levels of bioactive compound are easier to accept. If there is for a food no good un-modified alternative or if the need and advantage connected to the GMO-containing product is associated with human health, environmental advantages, or animal welfare the consumer acceptance is easier to obtain.
- Protecting technologies (encapsulation), enhancing levels of bioactive compounds via breeding, cultivation and genetic manipulation and optimisation of current technologies for bioactive compounds (matrix effects) are to be used for the development of functional foods. Use of novel non-thermal processes offer new interesting possibilities.
- Molecular separation technologies, biotechnology and synthesis are interesting technologies to be used in production of bioactive ingredients.
- The predictive modelling concept of different health aspects, that consists of a set of mathematical equations describing the fate of bioactive compounds in the food production chain, can be used as a tool for handling the variation throughout the chain in a quantitative, scientific way.
- We should use more 'the safe use history' data of bioactive compounds in the search for compounds for functional food production. With compounds that do not go under novel food regulation, but do not yet have a dietary requirement (like flavonoids) the daily intake must be derived from both the observed positive health effects and safe use history.
- Coupling the aspect of functionality with good sensory characteristics is essential for the acceptability of functional foods and business success.
- When producing functional foods the producer must consider, in addition to the general issues in food production, also the added physiological and/or health effects

function that the product should provide (the health claim). Strategic alliances between the food ingredient producers, manufacturers and academic research community are needed for the realisation of this strategy.

From the literature and as a result of the discussions during the two Workshops on the efficacy, claims, safety and legal aspects of functional foods, the following conclusions were drawn:

- Although various **definitions** of functional foods are described in the literature, the one formulated by ILSI Europe was considered a suitable working definition.
- The general concept in nutrition science is developing from a concept of 'adequate nutrition' (with recommended daily allowances to prevent nutritional deficiencies as a basis) to one of '**optimal nutrition**'. Functional foods may well fit into this development.
- **Classes of functional foods and ingredients** include fat replacers, products with antioxidants, probiotics/prebiotics, products with plant sterols, minerals/trace elements and foods for improving physical and mental performance.
- Although various definitions of **claims** have been formulated, any claim should be based on sound scientific evidence for **efficacy**.
- For assessing efficacy it is important to identify and validate **markers** that can predict potential benefits of functional foods. Preferably an effect on reducing risk for e.g. chronic diseases should be shown. If that is not possible an effect on a marker that has been shown to be related to a disease outcome may be sufficient.
- For **line extensions** of functional foods that are already on the market, in addition to the evidence that the active ingredient is present in the food consumed, other additional studies are required only when some specific matrix effects are envisaged (e.g. regarding interactions of the bioactive compound with other food components and effects on the bioavailability of the bioactive compound).
- Although no 100 % **safety** of any food can be guaranteed, (functional) food safety is always a well-balanced evaluation of risks and benefits. The risk associated with functional foods should not be higher than that of the corresponding conventional foods.
- A **case-by-case approach** for evaluating the efficacy and safety of functional foods include information on the composition, its (envisaged or actual) intake, its role in the diet and the identification of population target groups.
- Apart from existing legislation or regulations (international, e.g. within the EU and within the Netherlands), there is a clear need for a formal system for evaluating the claimed health effects of functional foods. This could well be based on the **Code of Conduct** of the Dutch 'Voedingscentrum' evaluated and changed to contain all for

functional food judgement needed essential elements: efficacy, effectiveness, safety and suggested claim. Pre-market-modelling and post-market study should, as essential parts of safety evaluation of functional foods, be demanded to be included to the dossier offered for evaluation.

- An approved claim on the package of a functional food should be accompanied by a distinct **logo** which informs the consumer about the scientifically justified claim and gives the producer a clear advantage over products/producers which try to associate their products with 'real' functional foods.
- **Post-marketing surveillance** of functional foods should be the responsibility of the company launching the product; for assessing the nutritional consequences of incorporating functional foods in the daily diet, the government (Health Council) was considered to be responsible.

Appendix 4: Research recommendations

From the results of the discussions during the workshop on **technology** and based on the recommendations with respect to 'research opportunities' as described in the ILSI report, the following lines of research can be recommended:

- Challenge to create new functional food components in conventional and raw materials and by the *novo* synthesis.
- The challenge to develop economically sound large scale processes to produce and purify known functional food ingredients from raw materials.
- The challenge of optimisation of functional food components and their functionality in raw materials and in foods.
- Challenge is also to secure the preservation or even increase of the functionality of the foods by optimising stabilisation, packaging and kitchen technologies.
- For the optimisation purposes there is an urgent need for the development of relevant markers of compound groups and monitor methods for both functional compounds and their functionality throughout the food chain and sensors on-line.
- Reliable and efficient communication strategies about food-health relationship and about the safety aspects of new technologies with the consumer should be developed.
- Regulatory barriers for the use of novel technologies should be removed by developing legislation.

From the results of the discussions during the workshops **health/claims and efficacy/safety** and based on the recommendations with respect to 'research opportunities' as described in the ILSI report, the following lines of research can be recommended.

- The *long-term effects of macronutrients replacers* on energy and fat balance and on body weight control.
- Evaluation of the *safety* of substances that modulate energy and glucose metabolism in short-term and long-term studies, because of the risk of disturbances in the lipid and glucose metabolism.
- Studies on the *qualitative and quantitative effects* of the uptake, distribution and metabolism of bioactive compounds, such as *flavonoids* and *carotenoids*.
- Studies on combined effects of synergy or antagonism between bioactive compounds, e.g. *antioxidants* and with other food components.

- Chemical analyses of the *content of non-nutritive antioxidants of foods* for food composition tables for epidemiological studies.
- Development and validation of *markers for oxidative damage* to key body structures that are non-invasive and acceptable in human volunteers, and validation of existing methods.
- Bioavailability and dose-response studies of validated and accepted markers as intermediate endpoints for testing the *efficacy of antioxidants* in intervention trials.
- Studies to quantify the *optimal levels of intake of antioxidants*.
- Studies on the effects of *interactions* of selected dietary components on various physiological functions.
- Establish *study designs* for *human intervention studies*, taking genetic polymorphisms, diet-gene interactions, life style effects and endocrine factors into consideration.
- Evaluation of the potential *toxicity* of very high intakes of *long-chain polyunsaturated fatty acids and antioxidants*.
- Developing and validating of *methods* to characterise *intestinal microflora*.
- Studies to *characterise the composition and activities of human colonic microflora* to investigate the effects of age and race and to explore the influence of different dietary habits.
- To investigate the factors that determine the *intra-individual variation* in response to *pro- and prebiotics*.
- Studies on the effect of *long-term changes* in the *composition of the colonic microflora* as influenced by dietary modulations, particularly by *pro- and prebiotics*.
- Developing and validating of *measures of cognitive function*.
- Testing of *multiple responses of cognitive function to nutritional stimuli* and assessing the *intra-individual variation* to identify vulnerable or sensitive individuals. In this respect, the development of genetic markers is a challenge.

Appendix 5: Lists of participants of the study meetings

“Kick off meeting” 22nd May 2000 in Vught

Bast, A. (Maastricht University)
Dekker, M. (Wageningen University)
Huizing, H. (NRLO)
Jongen, W. (Wageningen University)
Juriaanse, A. (NIZO Food Research)
Kalk, C. (TNO Food and Nutrition Research Institute)
Koenen, G. (KvW)
Langeveld, C. (RGO)
Mensink, R. (Maastricht University)
Ockhuizen, T. (Nutricom)
Papenhuijzen, H. (NRLO)
Plaami, S. (Wageningen University)
Saris, W. (Maastricht University)
Schilpzand, R. (Schuttelaar & partners)
Steins, J. (DMV International)
Vries, H. de (ATO-DLO)

Technology workshop 26th September 2000 in Utrecht

Dekker, M. (Wageningen University)
Frederix, J. (Honig)
Hollman, P. (Rikilt)
Huizing, H. (NRLO)
Jongen, W. (Wageningen University)
Juriaanse, A. (NIZO)
Kluijthoof, J.D. (DSM Gist Brocades)
Koenen, G. (KvW)
Kühn, C. (Foodlinkforum)
Meijer
Ockhuizen, T. (Stichting Zuivel, Voeding en Gezondheid)
Papenhuijzen, H. (NRLO)
Plaami, S. (Wageningen University)
Siemensma, A.D. (Quest International)
Verkerk, R. (Wageningen University)

Wichers, H. (ATO-DLO)

Claims and Health workshop 6th October 2000 in Utrecht

Dekker, M. (Wageningen University)
Dokkum, W. van de
Frederix, J. (Honig)
Hendricks, L. (Yakult)
Huizing, H. (NRLO)
Jongen, W. (Wageningen University)
Kalk, C. (TNO)
Katan, M. (Wageningen University)
Koenen, G. (KvW)
Kok, F. (Wageningen University)
Kromhout, D. (RIVM)
Langeveld, C. (RGO)
Mensink, R. (Maastricht University)
Plaami, S. (Wageningen University) (secr)
Poppel, G. van (Unilever Health Institute)
Sako, T. (Yakult)
Schilpzand, R. (Schuttelaar & Partners)
Vries, J. de (Friesland Coberco)

Efficacy/Safety workshop 10th October 2000 in Utrecht

Berg, H. van der (TNO)
Bladeren, P. van (TNO)
Bosman, W. (Health Council of the Netherlands)
Dekker, M. (Wageningen University)
Dokkum, W. van
Hendricks, L. (Yakult)
Huizing, H. (NRLO)
Jongen, W. (Wageningen University)
Juriaanse, A. (NIZO)
Kalk, C. (TNO)
Kok, F. (Wageningen University)
Kühn Abaunza, C. (Foodlink Forum)
Langeveld, C. (RGO)
Ockhuizen, T. (Stichting Zuivel, Voeding en Gezondheid)
Papenhuijzen, H. (NRLO)
Plaami, S. (Wageningen University)

Poppel, G. van (Unilever Health Institute)
Schaafsma, G. (TNO)
Shortt, C. (Yakult)
Vries, J. de (Friesland Coberco)
Wiel, J. van der (Gezondheidsraad)

Concluding meeting 6-7th November 2000 in Wageningen

List of participants 6th November

Berg, H. van der (TNO)
Bindels, J. (Numico Research BV)
Bosman, W. (Health Council of the Netherlands)
Dekker, M. (Wageningen University)
Dokkum, W.
Garssen, J. (RIVM)
Geluk, M. (NIZO)
Hendriks, L. (Yakult)
Hollman, P. (RIKILT)
Huizing, H. (Innovation Network, NRLO)
Jongen, W. (Wageningen University)
Kalk, C. (TNO)
Keyer J (RIKILT)
Kluijthoof, J.D. (DSM Gist Brocades)
Koenen, G. (KvW)
Kok, F. (Wageningen University)
Kromhout, D. (RIVM)
Kühnn, C. (Foodlinkforum)
Langeveld, C. (RGO)
Papenhuijzen, H. (Innovation Network, NRLO)
Peters, P.W.J. de (Keuringsdienst van Waren, Ministerie van VWS)
Plaami, S. (Wageningen University)
Sako, T. (Yakult Nederland)
Schipaanboord, A. (Consumentenbond)
Steijns, J. (Campina Melkunie)
Top, R. (VWS)
Verschuren, P. (Unilever)
Vries, H. de (ATO-DLO)
Vries, J. de (Friesland Coberco Dairy Foods, FCDF)
Wichers, H. (ATO-DLO)

Wiel, J.A.G. (Gezondheidsraad)

List of participants 7th November

Berg, H. van der (TNO)

Bindels, J. (Numico Research BV)

Bosman, W. (Health Council of the Netherlands)

Brussaard, T. (TNO)

Dekker, M. (Wageningen University)

Dokkum, W.

Garsen, J. (RIVM)

Geluk, M. (NIZO)

Hendriks, L. (Yakult)

Huizing, H. (Innovation Network NRLO)

Jongen, W. (Wageningen University)

Kalk, C. (TNO)

Keijer, J. (Rikilt)

Kluijthoof, J.D. (DSM Gist Brocades)

Koenen, G. (KvW)

Kok, F. (Wageningen University)

Kühn, C. (Foodlinkforum)

Langeveld C. (RGO)

Papenhuijzen, H. (Innovation Network, NRLO)

Peters, P.W.J. de (Keuringsdienst van Waren, Ministerie van VWS)

Plaami, S. (Wageningen University)

Sako, T. (Yakult Nederland)

Saris, W. (Maastricht University)

Verschuren, P. (Unilever)

Vries, H. de (ATO-DLO)

Vries, J. de (Friesland Coberco Dairy Foods, FCDF)

Wichers, H. (ATO-DLO)

Wiel, J.A.G. (Gezondheidsraad)

<i>Comparative claims</i>	Such as Reduced; Less than; Fewer; Increased; More than.
<i>Health claim</i>	'Any statement, suggestion or implication in food labelling and advertising that a food is in some way beneficial to health, and lying in the spectrum between, but not including, nutrient claims and medical claims' (<i>the Food advisory Committee, UK</i>). <i>In the USA, a health claim refers to any statement 'that expressly or by implication characterises the relationship of any substance to a disease or health-related condition' . In the UK therefore, a health claim related to a disease would be considered as a medical claim whereas in the USA it would be regarded as a 'health claim' . According to EU-law (directive 2000/13/EG) 'Labelling must not attribute to any foodstuff the property of preventing, treating or curing a human disease, or refer to such properties.'</i>
<i>Nutrient function claims(Codex Alimentarius) = 'Type A' claims (ILSI) = 'Enhanced function' claims (ILSI) = structure/function claim (in USA)</i>	Claims referring to specific beneficial effects of nutrients and non-nutrients on physiological, psychological functions or biological activities beyond their established role in growth, development and other normal functions of the body. They make no reference whatsoever to a specific disease, pathological state or abnormal condition. Examples are: 'Calcium might help the development of strong bones and teeth', 'Contains folic acid which contributes to the normal development of the foetus' or 'High in carbohydrate to improve endurance, performance'.

<i>'Reduction of disease risk' = Type B claims (ILSI)</i>	Refer to reduction of disease risk, related to the consumption of a food or food component that might help reduce the risk of a specific disease or condition because of specific nutrients or non-nutrients contained within that food.
<i>Medical claim</i>	claim that attributes to the property of preventing, treating or curing a human disease, or refers to such properties
'Code of Conduct'	'Gedragscode wetenschappelijke onderbouwing Gezondheidseffecten ten behoeve van Gezondheidsclaims voor eet- en drinkwaren 1998' of the Dutch 'Voedingscentrum'. 'Code of conduct' is set up on a voluntary basis and is an agreement between industry, consumers organisations, (nutrition) educators, science and supported by government, but has no official legal status. In it a procedure is described for the evaluation of functional foods regarding health claims. The evaluation of a new functional food is carried out on request of the producer of the product.
COS	Centrum voor Onderzoek en Statistiek
Effectiveness	Measures the actual effect of a product under average conditions among the population at large.
Efficacy	Measures the desired effect of a product under ideal conditions and thus answers the question 'Can the product produce the effect as claimed?'
FDA	U S Food and Drug Administration
Functional food	A food by sound scientific research 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. Functional foods must remain foods and they must demonstrate their effect in amounts that can normally be expected to be consumed in the diet.
Functional food science	Refers to new concepts in the science of nutrition that will stimulate research into the physiological effects of non-nutritive compounds and of nutrient intake beyond those of preventing deficiencies and to the development of functional foods. In functional food science health and nutrition sciences are integrated with food technology to produce foods with measurable health benefits.
GCPs / GEPs	Good practices concerning the collection and analysis of human data – clinical and /or epidemiological practices
GLPs	Good laboratory practices
GMPs	Good manufacturing practices
GMO	genetically modified organism

ILSI	International Life Sciences Institute
KAG	'Kode voor de Aanprijzing van Gezondheidsproducten'
Model, modelling	A model can be defined as a hypothesis about how a system works or responds to changes in its inputs. Models can be described in mathematical language, with equations and input variables, based on empirical or theoretical considerations. The purpose of a model is to represent a system of interest as accurately as is necessary for its intended application.
<i>Deterministic model</i>	Models in which point estimates are used and variability and uncertainty in the input variables are not taken into account. (For example in pre-market modelling variability refers to real differences between and within populations, individuals and products. Uncertainty has to do with lack of knowledge; the uncertainty will be less if more data can be collected.)
<i>Probabilistic model</i>	Models in which information about the distribution of the input variables is used. The uncertainty and variability in input variables is propagated through the model to obtain a quantitative insight into the range of possible model outcomes and the probability for each of these model outcomes.
<i>Monte Carlo simulation</i>	A probabilistic modelling method characteristic to which is that the result of analysis is not a point estimate, but a distribution of possible model outcomes. After constructing (conceptually and mathematically) a model it is determined which variables are essential for the calculations (input variables). To the input variables a distribution is attributed, based on earlier experience and/or expert opinion.
MU	Universiteit Maastricht / Maastricht University
Non-nutrient	Food component, that (mostly) exist in small quantities in our food and have only limited caloric value and are not either macro or micro nutrients (e.g. dietary fibre, secondary plant metabolites etc.). They can, however, have biological activity via modulation of physiological functions of the body.

Novel food	<p>food that has not been used for human consumption to a significant degree and falls into some of the following categories:</p> <ul style="list-style-type: none"> • containing or is consisting of genetically modified organisms (GMOs) or • is produced from GMOs, although not contain them, or • contains a new or intentionally modified primary molecular structure • consisting of or isolated from micro-organisms, fungi or algae, • consisting of or isolated from plants and food ingredients isolated from animals, except for foods and food ingredients obtained by traditional propagating or breeding practices and having a history of safe food use • to which have been applied a production process not currently used, where that process gives rise to significant changes in the composition or structure of the foods or food ingredients which affect their nutritional value, metabolism or level of undesirable substances
Nutraceutical	food supplements, herbs and herb medicines
NRLO	Nationale Raad voor Landbouwkundig Onderzoek / National Council for Agricultural Research
NWO	de Nederlandse Organisatie voor Wetenschappelijk Onderzoek / The Netherlands Organisation for Scientific Research
Predictive modelling applied to health aspects	modelling concept of health aspects consisting of a set of mathematical equations describing the fate of bioactive compounds in the food production chain
Pre-market modelling of functional foods	Modelling the fate of bioactive component (in functional food) in different food patterns and corresponding effects (beneficial and non-beneficial). Different modelling techniques can be used to answer questions of several complexities.
<i>Simulation study in pre-market modelling</i>	Currently the intake of a food component is calculated by multiplying the amount of food eaten by the concentration of the food component in the food. In simulation study the concentration of a certain ingredient or component is changed and the calculation is repeated.
<i>Scenario study in premarket modelling</i>	Complicated simulations involving changes in more foods and in varying combinations at a time.

Post-market surveillance (PMS)	Research on amount and pattern of consumption, determination of the nature and degree of expected effects (both beneficial and non-beneficial), and unexpected effects after a new food has been launched.
RGO	De Raad voor Gezondheidsonderzoek / Council for Health Research
RIVM	Rijksinstituut voor volksgezondheid en milieu/National Institute of Public Health and the Environment
Technology platform	The forum where company's strategy to link knowledge and information held in different departments and functions together are discussed.
SCOOP	Scientific co-operation (within EU)
'virtual cells'	testing compound effects on cell level by computer modelling
WU	Wageningen Universiteit /Wageningen University

