



Position paper: Functional foods

Functional foods can be defined as foods that contain one or more added ingredients to provide a positive health benefit, over and above the normal functions of food to provide nutrients, satisfy physiological and psychological hunger and provide pleasure from eating.

This definition excludes vitamins and minerals added to foods to replace losses in manufacture. For the purposes of this paper I will also exclude vitamins and minerals added to breakfast cereals, which were originally intended to provide the micronutrients that would have been obtained from a traditional cooked breakfast. Similarly I will exclude vitamins A and D added (by law in UK) to margarine to provide the vitamins that would have been obtained from butter.

The concept of functional foods was developed in Japan in the 1980s, with a formal definition of “foods for specified health use” (FOSHU) in 1991, accompanied by a regulatory system to approve the statements made on labels and in advertising, based on scientific evaluation of the evidence of efficacy and safety [1]. At the turn of the century the European market for functional foods was some £830 million and at the time was predicted to increase to £1.6 billion by 2010 [2] – this may well have been an underestimate.

As with so many areas, while there may be good evidence of *potential* benefits of some functional foods, and well-conducted trials show improvement in biomarkers and risk factors, as yet there is little evidence of improved health or increased lifespan in most cases.

Food fortification to prevent deficiency

When a micronutrient (vitamin or mineral) deficiency is widespread in a population, a common approach is to enrich or fortify a staple food. The problem here is that if enrichment is voluntary, so that consumers have a choice of whether to buy the fortified or unfortified product, it is likely that the most vulnerable groups of the population will not be reached. However, if enrichment is mandatory then political problems of freedom of choice arise. It is noteworthy that despite the excellent evidence that fluoride reduces dental decay very significantly, fluoridation of water supplies is not universal in Britain, because of (unfounded) fears of “mass medication”.

Iodine and goitre prevention

The earliest example of food enrichment to meet a public health problem was the use of iodine to prevent goitre; in 1900 it was added to chocolate in Switzerland, as a way of meeting the iodine needs of the children - most vulnerable group. However, the most popular vehicle for iodine enrichment is table salt. In some countries iodized salt is required by law either throughout the country or in vulnerable regions; in others it is optionally available. In the Netherlands and Australia, by law, bread must be baked using iodized salt.

There is no doubt that iodization of salt is effective in preventing goitre (and the more serious problem of goitrous cretinism in infants born to iodine deficient mothers). Four years after the introduction of iodization in Guatemala in the early 1950s the prevalence of goitre had fallen from 38% to 5%. Similarly impressive reductions in the prevalence of iodine deficiency disease have been reported from other countries following iodization.

There is, however, a problem with widespread iodization. Adults who have compensated for inadequate iodine deficiency by developing goitre (i.e. enlarging the thyroid gland so that it produces an adequate amount of thyroid hormone) are at risk of hyperthyroidism when their iodine intake increases.

Folic acid and the prevention of neural tube defects

There is excellent evidence [summarised in references 3 and 4] that 400µg of additional folic acid daily halves the number of babies born with spina bifida and other neural tube defects – and this does not include the relatively large number of affected births prevented by therapeutic termination of pregnancy following ante-natal screening. In USA (and a number of other countries) flour has been fortified by law with folate for more than a decade, and there has been a decrease of 27 – 50% in the number of babies born with neural tube defects [4].

Until now, fortification of flour has not been mandatory in UK, but the advice has been that women who are planning a pregnancy should take supplements, or choose folic acid enriched foods that are available. The problem is that half of births are not planned, and the critical period for folate intake (when the neural tube closes) is between 21 – 28 days of gestation – before the woman knows she is pregnant. Despite more than a decade of publicity for folic acid supplements, there has been no decrease in the number of pregnancies affected by neural tube defects in UK or other EU countries where supplementation is recommended and fortification is not mandatory [4].

The Food Standards Agency in UK has now recommended that flour should be enriched with folic acid, and has published a list of options [5]. However, intakes of folic acid above about 1000µg /day pose a hazard to two groups of the population: the elderly, in whom it might mask early signs of vitamin B₁₂ deficiency due to atrophy of the gastric mucosa with increasing age; and people with epilepsy, since high intakes of folic acid antagonise some anticonvulsant medication. Therefore a balance must be struck in deciding the level of fortification, to ensure benefit to unborn children without putting vulnerable people at risk of excessive intake. The FSA advice is that if flour is to be enriched with folate then voluntary enrichment of other foods should cease [4,5].

... and cardiovascular disease?

There is excellent evidence that an elevated blood concentration of homocysteine is a risk factor for atherosclerosis and stroke. There are eminently plausible biological mechanisms to implicate homocysteine as a causative factor in these diseases, and in people genetically at risk of elevated homocysteine relatively high intakes of folate lower the blood concentration significantly [6].

Possibly as a result of mandatory enrichment of flour in USA and Canada, there has been a significant fall in stroke mortality [7], although it is not clear how much this is due to reduced incidence and how much to a reduced case-fatality rate [4]. Randomised controlled trials suggest that folate is beneficial in reducing stroke incidence – the HOPE2 trial showed a 25% reduction in stroke mortality with supplements of folate (and other vitamins involved in homocysteine metabolism) [8]. In another intervention trial, although there was a significant reduction in plasma homocysteine, there was no reduction in death from myocardial infarction, other cardiovascular disease, or, indeed, all cause mortality [9].

This raises two sets of questions:

- Is the theory wrong – are the biological mechanisms that implicate homocysteine incorrect? Is homocysteine a marker of atherosclerosis rather than a cause? It may be that elevated plasma homocysteine is a result of atherosclerosis affecting the kidney, so that its excretion is impaired.
- Is it too early to see results? Folic acid enrichment has only been mandatory in USA and Canada for a decade, and the people currently dying from cardiovascular disease have long-established atherosclerosis. It is presumably younger people who will be protected if high intakes of folate are protective. Furthermore, the RCTs [8,9] were secondary prevention trials, in people who already had cardiovascular disease or had already suffered a heart attack.

Intestinal bacteria – prebiotics, probiotics and synbiotics

It is a sobering thought that we host ten times more bacteria in the intestinal tract than there are cells in the human body. Some of the 100 or more species are pathogenic, some are harmless commensals, and some (especially the lactic acid producing bacteria) are beneficial, either producing a variety of compounds that prevent the growth of pathogenic organisms or fermenting resistant starch

and dietary fibre to provide short-chain fatty acids that are the preferred fuel for intestinal mucosal cells and may have anti-cancer activity.

The main lactic acid producing bacteria of interest are *Lactobacillus* and *Bifidobacteria* spp., and there is evidence for beneficial effects of lactic acid bacteria in controlling allergies, preventing or curing constipation and generally maintaining gastro-intestinal health [10,11].

Can we modify intestinal bacteria to increase the population of beneficial organisms?

There are two approaches to this: consumption of beneficial bacteria (collectively known as probiotics) and consumption of non-starch polysaccharides (and especially short-chain oligosaccharides), which provide a substrate for fermentation by the probiotic bacteria, and are therefore known as prebiotics. The combination of the two, probiotic bacteria and prebiotic carbohydrates, is known as a synbiotic.

Consume the bacteria – probiotics

Elie Metchnikoff was co-recipient (together with Paul Ehrlich) of the 1908 Nobel Prize in Physiology or Medicine for his discovery of cell-mediated immunity and phagocytosis. From about 1900 until his death at what was then the advanced age of 71 he was interested in ways of increasing longevity and, inspired by the reported longevity of people in the Balkans who drank fermented milk, he advocated the consumption of lactic acid-producing bacteria in soured milk and yoghurt.

Inspired by Metchnikoff, the Japanese microbiologist Minoru Shirota (who was 83 years old when he died in 1982) isolated a strain of *Lactobacillus casei* that could not only survive the acid conditions of the stomach and thrive in the intestinal tract, but could out-compete potentially harmful organisms. In 1935 he started selling a yoghurt-like drink containing this organism under the name Yakult. According to the Yakult company's website, "each tiny bottle [65 mL] of Yakult contains 6.5 billion active bacteria of the strain *Lactobacillus casei* Shirota" [10]. Yakult was introduced to the European market in 1994, from a factory with a production capacity of 720,000 bottles per week. This one production site has a current capacity of 10 million bottles a week, and the company claims that in 2007 Yakult "is enjoyed daily by 25 million people in 28 countries around the world and this number continues to grow" [10]. Danone [11] produce two probiotic yoghurts: Activia, which contains *Bifidobacteria* and Actimel, which contains *L. casei*. Sales of Actimel are reported to have reached €1.4 billion in 2006 [12]. Both companies sponsor a considerable amount of research into the effects of changing intestinal bacterial flora, and are generous sponsors of scientific meetings.

We cannot know whether the longevity of Metchnikoff and Shirota was due to their consumption of lactic acid bacteria, and any RCT will presumably take 70 – 80 years (or longer) to produce results. However, what we do know is that you have to keep drinking the probiotic yoghurt. The beneficial strains of *Lactobacillus casei* and *Bifidobacterium* spp. do not seem to be able to establish stable colonies in the intestinal tract [13].

Feed the bacteria – prebiotics

It has long been known that something present in human milk (but absent from cows' milk) that promotes the growth of *Bifidobacteria* and other beneficial species, and that the intestinal bacterial flora of breast fed babies differed from that of bottle fed babies. What was originally called the bifidus factor is now known to be a mixture of prebiotic oligosaccharides – carbohydrates that are not digested in the small intestine, but provide a substrate for bacterial fermentation in the large intestine. A number of foods are now available that contain added prebiotic carbohydrates, including drinks, yoghurts, biscuits, breakfast cereals and margarines. Does encouraging the growth of lactic acid bacteria have any effects on health?

There is a good evidence for the effects of some prebiotics in alleviating constipation. They are also useful in treating hepatic encephalopathy, which is due to ammonia intoxication as a result of liver failure – here the effect is due to acidification of the gut contents, so that ammonia diffuses from the blood stream into the gut, and is trapped as ammonium salts, which cannot cross back into the bloodstream [14]. The evidence is less good for the prevention of colon cancer, intestinal infection, and recurrence of inflammatory bowel disease, but a number of trials have suggested that prebiotics can prevent colonisation of the intestinal tract with pathogens such as *Clostridium difficile* and

Helicobacter pylori [14], although there are beneficial effects against the development of experimental colon cancer in animals [15]. There is also evidence that prebiotics can modulate various properties of the immune system, especially the gut-associated lymphoid tissues (GALT) [16], and enhance calcium absorption [17].

Although inulin and other oligosaccharides have a lipid-lowering effect in experimental animals, the results of human trials have been mixed. Williams and Jackson [18] suggest that this is because it is not possible to feed human volunteers amounts of prebiotics equivalent to those used in experimental animals because of the gastrointestinal discomfort experienced by most people consuming more than about 15 g/d.

Perhaps the situation is best summed up by this quotation from Cummings and Macfarlane [19] “prebiotic carbohydrates clearly have significant and distinctive physiological effects in the human large intestine, and on the basis of this it is *likely* that they will *ultimately* be shown to be beneficial to health” (my italics).

Changing dietary fat and lowering cholesterol

For half a century or more we have known that elevated serum cholesterol, and especially low density lipoprotein cholesterol, is a major risk factor in atherosclerosis and coronary heart disease. There are excellent biological mechanisms to explain this. Low density lipoprotein that has not been cleared by the liver (either because the liver has enough cholesterol for its needs, and so down-regulates the uptake mechanism or because the lipoprotein has been oxidised in the circulation, and so is not recognised by the liver receptor) is taken up by macrophages, which infiltrate the arterial wall, die and lay down fatty plaques that occlude the arteries [20].

The results of a series of experiments in the 1950s and 1960s in which volunteers were fed diets with different amounts of saturated or polyunsaturated fats to replace mono-unsaturated fat showed that serum cholesterol increases proportionally to 2 x the intake of saturated fat and decreases proportionally with the polyunsaturated fat intake. Similar studies showed that dietary cholesterol intake was less important, increasing serum cholesterol proportionally to the square root of cholesterol intake [21,22].

An interesting whole country experiment has been conducted in Mauritius. In 1987 the government, concerned by the high incidence of coronary heart disease, changed the formulation of the main cooking oil from one based on palm oil (and hence high in saturated fat) to one based on soya bean oil (providing 30% polyunsaturated fat). Total fat and cholesterol intakes were unchanged, and after 5 years average serum cholesterol concentrations had fallen significantly [23]. However, there has been no report as yet of any change in cardiovascular mortality (checked with a MedLine search on 15/8/2007). Perhaps even 20 years is not long enough to see any beneficial effects on younger people.

Plant sterols and stanols to lower serum cholesterol

Average daily intakes of cholesterol from the diet are between 300 – 600 mg /day; in addition to this, some 2000 mg of cholesterol is secreted each day in the bile, much of which is reabsorbed. This means that anything that will reduce cholesterol absorption from the small intestine will have a much larger effect on whole body cholesterol (and hence serum cholesterol) than would be expected from the dietary intake alone.

Cholesterol is absorbed together with other lipids in the diet in lipid micelles, and is then esterified with fatty acids before being incorporated into chylomicrons that enter the circulation. Any cholesterol in the intestinal mucosal cells that is not esterified is rapidly exported from the cell back into the intestinal lumen, by an active transport process. Analogues of cholesterol, such as the plant sterol β -sitosterol and the stanols, both compete with cholesterol for inclusion in the lipid micelles and also inhibit the enzymes that esterify cholesterol, so that less enters the circulation.

There is abundant evidence that consumption of plant sterols and stanols lowers low density lipoprotein cholesterol, and the effect is additive to that of statins, the drugs that inhibit cholesterol

synthesis [24,25]. A variety of sterol- or stanol-containing low fat spreads, yoghurts, drinks and cream cheeses have been marketed. There are also chewable sweets containing Benecol stanol esters [26]. Lowering serum cholesterol certainly reduces the risk of myocardial infarction, and there is no evidence that plant sterols and stanols enter the circulation or contribute to atherogenesis (apart from rare children with sitosterolaemia, a genetic defect of the intestinal sterol exporting protein, who develop severe atherosclerosis at a young age).

Functional foods containing plant sterols and stanols seem to “do what it says on the label”. However, a review by Muldoon [27] of intervention trials to lower serum cholesterol (before the introduction of statins or plant sterols and stanols) showed that while there was a pleasing 15% reduction in death from cardiovascular disease, there was no reduction in overall mortality, and a 75% increase in death that was not illness related (i.e. accident, murder and suicide). This has never been satisfactorily explained.

Superfoods

The concept of superfoods was developed in the USA in 2003-4 and was introduced in Britain by an article in the Daily Mail on December 22nd 2005 [28]. Superfoods are ordinary foods that are especially rich in nutrients or antioxidants and other potentially protective compounds, including polyunsaturated fatty acids and dietary fibre. Scanning through a handful of websites [28 - 31] thrown up by a Google search for “superfoods” gives the following list:

almonds, apples, avocado, baked beans, bananas, beetroot, blueberries, Brazil nuts, broccoli, Brussels sprouts, cabbage, carrots, cocoa, cranberries, flax seeds, garlic, ginger, kiwi, mango, olive oil, onions, oranges, peppers, pineapple, pumpkin, red grapes, salmon, soy, spinach, strawberries, sunflower seeds, sweet potato, tea, tomatoes, watercress, whole grain seeded bread, whole grains, wine, yoghurt.

There are very few surprises in this list. Most of these are foods that nutritionists and dietitians have talked about for years as being nutrient dense – i.e. they have a high content of vitamins and minerals / 100 Calories. The nuts, seeds and olive oil are an exception, but they are all good sources of polyunsaturated fatty acids.

The labelling and marketing of the foods as superfoods seems disingenuous (or a clever marketing strategy), but if such marketing leads people to eat more fruit and vegetables and reduce their saturated fat, salt and sugar intake then it can only help to reinforce the message that the nutrition and public health communities have been preaching for more than a quarter of a century.

Position paper prepared by David A Bender and approved by the HealthWatch committee 11/7/2007

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