Why the European Food Safety Authority was right to reject health claims for probiotics

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Abstract

Probiotics are microbes that are claimed to promote health and well-being when added to foods. However, the European Food Safety Authority (EFSA) has so far advised negatively about health claims for probiotics. Companies and scientists have protested against these rejections, sometimes in vigorous language. I argue that EFSA could not have acted differently, given EU regulations and the lack of convincing evidence for some of the claimed effects of probiotics on human health and well-being. One EU regulation that makes it hard to demonstrate the benefits of probiotics is the prohibition of medical claims, i.e. claims that a food prevents or cures a disease. If this prohibition did not exist, manufacturers of nutritional treatments might circumvent the costly procedures required for drugs, and market their products to ill people without thorough proof that they are effective and safe. However, the prohibition is also a legal fiction, because promotion of health and prevention of disease is largely the same thing. EFSA has recently indicated that it will allow health claims based on the ability of probiotics to reduce infections. To a certain extent, this abolishes the distinction between health claims and medical claims. It remains to be seen if probiotics producers can convince EFSA that their products prevent or cure infections and other diseases in humans.

Keywords: health claims, immune response, EU regulation, gut, probiotics, disease, infection

1. Introduction

Anger in Amsterdam

On December 2, 2010, representatives of the European Food Safety Authority (EFSA) met in Amsterdam with scientists and representatives of the food industry to discuss foods that may promote gut health. EFSA had rejected all health claims for such foods – or rather, advised negatively about such claims to the European Commission. The meeting aimed to discuss the scientific requirements for health claims related to gut and immune function (EFSA-NDA, 2011a). The report of the meeting describes it as ‘a good opportunity to exchange views’, but the webcast shows angry scientists and marketeers uttering strong reproaches to EFSA (EFSA, 2010). Similarly vehement language was recently used by Reid in this Journal:

‘the European Food Safety Authority (EFSA) has created a panel that has ignored good science, over-ridden peer-reviewed medical studies, and seems intent on breaking the back of a validated approach to infectious disease management, namely probiotics’ (Reid, 2011).

Elsewhere, Reid has stated:

‘s much good research has stopped or been undermined by a group of people with apparent big egos and an axe to grind. Shame on them for not giving direction and for seeing the world through pharmaceutical tainted glasses’ (Starling, 2011).
Other interested parties are no less angry, even if they maintain decorum (Starling, 2010). Understanding these frustrations requires some insight into probiotics and into the EU regulations for health claims.

**Probiotics**

Probiotics are bacteria that are added to food products to promote health and well-being. One of the oldest of such products is Yakult, a fermented dairy drink with the bacterium *Lactobacillus casei* Shiruta. Large amounts of money are at stake in probiotics. The turnover of Actimel, a probiotic yoghurt drink produced by the French multinational Danone, was estimated at € 1.4 billion (i.e. thousand million) for 2006 (Market Research, 2007) and is probably higher now. Profit margins for probiotic dairy drinks are also significantly higher than for ordinary yoghurt or milk (Class Action Complaint, 2008). For instance, the retail price of Yakult in the Netherlands is € 4.79 per litre, as opposed to € 0.75 for regular yoghurt. The difference is substantial even when extra marketing and packaging costs are taken into account.

Probiotics also offer a unique legal advantage over other food ingredients with health claims. Healthy food ingredients such as vitamins or minerals are rarely patentable. In contrast, it is quite feasible to produce unique new bacterial strains. These may be sufficiently similar to common ‘yoghurt’ bacteria to gain the status of ‘food grade’, but sufficiently different to be patentable. Food marketers therefore stress the uniqueness of their probiotic strains, and give them fancy names such as *Lactobacillus immunitas* or *Lactobacillus defensis*.

**The EU regulations for health claims**

Consumers want foods that promote health and well-being and are willing to pay a premium for such foods. This has led to an avalanche of often poorly substantiated health claims. The European Union therefore decided that health claims should be vetted and approved centrally, and it asked EFSA to provide a scientific opinion on thousands of candidate claims. These opinions are written by groups of scientists who have volunteered to serve on specialised EFSA panels. Such opinions are based on the dossier submitted with the claim and on the relevant EU regulations. Further details can be found in various EFSA documents (EFSA-NDA, 2011b).

By July 2011, EFSA had published opinions on some 3,000 claims, and 80% of them were judged to be insufficiently substantiated. That still leaves hundreds of claims that were considered valid, and together these ‘approved’ claims are a rich source of information about what nutrition can achieve for human health. However, none of the approved claims dealt with probiotics. EU law demands proof of a beneficial physiological effect for a claim to be allowed (EC, 2007). In many of its opinions on probiotics, EFSA stated that the outcomes measured — e.g. changes in the concentrations of certain classes of white cells in blood — did not equate a beneficial physiological effect.

Why did research on probiotics focus on outcomes that are considered irrelevant or at best insufficient by the European authorities?

2. The problem with claims for probiotics

There are two possible explanations why manufacturers presented irrelevant effects of probiotics in their claim submissions to EFSA. One is that the product has no relevant effect. Imagine a hypothetical case where a manufacturer seeks to claim an effect on human ‘defence mechanisms’, i.e. on resistance to infections. Studies commissioned by the manufacturer may fail to show that the product reduces the risk of e.g. influenza. Such studies usually also measure the concentration and activity of various types of white cells and proteins in blood involved in immune function, and some of these concentrations and activities might change upon consumption of probiotics. This can be used to justify advertisements for probiotics that refer to ‘defence mechanisms’ in a general sense, without specifying exactly what the product does. Such claims based on a change in the concentration or activity of some cell or protein were rejected by EFSA, because of a lack of the ‘beneficial physiological effect’ demanded by EU law.

Cells and proteins are also less credible than disease occurrence as an outcome because there are so many cells and proteins in blood, and multiple statistical comparisons may produce spurious significances. When measurements are made on 10 blood proteins simultaneously, there is a 40% chance in conventional statistical testing that at least one of these proteins will show a significant ($P<0.05$) effect of the probiotic. With 45 proteins or cells, the chance of a ‘significant’ change in one of them is 90%, even if the outcomes are random numbers$^1$. I do not know whether EFSA scientists had this issue in mind when they rejected claims based on cell and protein changes, but it is a well-known problem that is frequently discussed in the scientific literature (Ioannidis, 2005).

**When probiotics do work, it may be forbidden to say so**

The second problem facing manufacturers is that, even if a probiotic does prevent influenza, they are not allowed to advertise this benefit. Under EU law, it is illegal to state to consumers that a food can prevent, treat or cure a disease (EC, 2000). A similar prohibition of ‘medical’

\[ 1 - (1 - 0.05)^{10} = 0.40 = 40\%; \quad 1 - (1 - 0.05)^{45} = 0.90 = 90\% . \]
claims for foods is incorporated into the national laws of most countries. Therefore EFSA is not allowed to approve such medical claims.

Scientifically, the ban on medical claims for foods does not make sense. It is an established fact that foods and food components can prevent, treat and cure diseases; that is what nutrition science is about. Lemons cure scurvy, and folic acid (vitamin B11) prevents neural tube defects, to give just two examples (Shils et al., 2006). Therefore the ban on medical claims for foods is a legal fiction, but it is a useful and indispensable fiction because it protects patients from treatments that are ineffective or unsafe (Coppens et al., 2001). Before the European Medicines Agency approves sales of a new medical drug, it demands vast amounts of evidence for efficacy and safety. The costs of producing such evidence may exceed a thousand million Euro. Regulations for health claims for foods should not provide a detour by which those costly rules can be circumvented. Any manufacturer who claims that his product prevents influenza must therefore prove efficacy and safety to the European Medicines Agency rather than to EFSA, regardless whether it is a new vaccine or a probiotic yoghurt. These legal limitations are another explanation why advertisements for probiotics speak of ‘defence’ and ‘healthy intestines’; and never state in so many words that the product prevents colds or cures constipation.

There is a clear rationale for the prohibition of medical claims for foods, but it does leave both EFSA and food producers with a paradox. EU regulations demand that a claim is a statement about the food ingredient and its ‘beneficial physiological effect’ on the body (EFSA, 2008). But how can a physiological effect be beneficial if it does not cure a disease or reduce the risk of becoming ill? The objective of the ban on medical claims for foods is laudable, but it denies reality because health and disease are often two sides of the same coin.

Where does the evidence for probiotics stand?

Producers of probiotics have protested that they cannot prove efficacy of probiotics against disease outcomes when EU regulations forbid medical claims. However, though there is a ban on advertising medical effects of probiotics, there is no ban on investigating and publishing such effects. Published evidence that probiotics prevent or cure disease is mixed. There is abundant evidence that consuming probiotics causes an increase in the number of probiotic bacteria in the intestines and faeces, but EFSA rightfully did not consider this a beneficial effect as such. Many claims submitted to the EU alluded to strengthening of the immune system and the defence against infections. Those claims were supported by measurements of various cells and proteins in blood, but such changes are beneficial only if they lead to fewer colds, influenza or intestinal tract infections, and the evidence that probiotics can do that is mixed. There is some evidence that certain probiotic strains shorten the duration of diarrhoea (Allen et al., 2010; Johnston et al., 2011; Rowland et al., 2010). Evidence for an effect on respiratory or genito-urinary infections are thought promising but inconsistent (Abad and Safdar, 2009; Hao et al., 2011; Rowland et al., 2010), and evidence for a reduction of allergic rhinitis and asthma (Vliagoftis et al., 2008) or constipation (Chmielewska and Szajewska, 2010; Katan, 2008) is shaky or absent.

Given these gaps in the evidence, the protestations of probiotics producers and allied scientists strike me as less than convincing. For instance, advertisements for probiotics commonly suggest that they relieve constipation. If that is true it should be easy to prove. All it takes is giving one hundred volunteers a probiotic yoghurt for a month and another one hundred volunteers an indistinguishable placebo, have them record their frequency and ease of defecation, and measure moisture content and hardness of faeces. The costs of such a study are negligible compared with the advertising budgets for probiotics. I expect that EFSA scientists would have been only too happy to see evidence that probiotics actually prevent or improve constipation, and would not have been too finicky about the distinction between health and medical claims here, but no convincing evidence was submitted.

3. New developments

Medicalisation of nutrition research

As a follow-up to the meeting in Amsterdam, EFSA published new guidance on the scientific requirements for health claims related to gut and immune function (EFSA, 2011). That guidance paper does not maintain a strict boundary between health claims and medical claims. EFSA now explicitly accepts the frequency and severity of intestinal and respiratory tract infections as outcomes to be considered in the evaluation of claims. In addition, research does not need to be restricted to healthy people but may also include subjects with intestinal ailments.

This guidance document should solve the problem of probiotic producers and allied scientists that they do not know which outcomes are needed to get a claim approved, and that they cannot present disease outcomes as evidence. At the same time, it confirms their fear of being sent down the pharmaceutical path. Proving the efficacy and safety of a food component can become expensive if the endpoint is the occurrence of a real disease (Biesalski et al., 2011). Cost may not be the only reason why producers of probiotics might be reluctant to sponsor studies with real clinical endpoints. A definitive, high quality study of the effect of probiotics on common infections will cost only a fraction of the funds currently spent on advertising. However, there is
a risk that such a study will fail to provide proof of efficacy, and that might seriously harm sales.

Manufacturers are thus faced with a devilish dilemma. If they cannot produce convincing clinical proof for an effect of probiotics on constipation or infection, advertising which suggests such effects will come under increasing pressure from the authorities in EU nations. However, if they attempt to produce such proof and find that the product does not live up to expectations, sales might suffer. I speculate that most manufacturers will consider the risk of an unfavourable outcome of a definitive clinical trial unacceptable, and will avoid doing such studies. It might be a better strategy to try and circumvent advertising curbs by changing the language used and by switching marketing efforts to other media, such as sponsored websites, apps and Facebook.

Effect of EU law on research into health-promoting foods

Food industries have expressed concern that the demands of the EU claims regulation will stifle innovation of healthy ‘functional’ foods. New research might still yield truly innovative foods now that the EU has placed the bar so high, but the research efforts needed are enormous and the chance of a pay-off is slim. Food companies might prefer to move their research and marketing efforts to other continents where demands for proof of efficacy are less stringent.

There is also a risk that the demand for convincing scientific proof will harm scientific integrity. There are many examples in pharmaceutical research of how pressure from the manufacturer of a new drug led to manipulation and distortion of data (Angell, 2008). The effects of foods or food components on health are also more favourable in publications where the producer of the food had funded the research (Lesser et al., 2007). Scientists who investigate probiotics may need a favourable outcome to ensure their future funding or employment, and the pressure to deliver results that support a health claim might lead to manipulation of data and to selective statistical analyses. It is easier to manipulate outcomes in food than in drug research because research on foods is subject to less stringent controls and protocols.

Probiotics producers thus face a double challenge, not only to produce favourable results but also to maintain credibility. The recent exchanges between industry and EFSA may have clarified what is needed to get a probiotic claim approved in the EU, but it has not made life easier for producers.

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