

What is a health benefit? An evaluation of EFSA opinions on health benefits with reference to probiotics

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OPINION PAPER

Abstract

Probiotics are microorganisms that have a beneficial effect on the health of the host. However, before these effects can be referred to as beneficial to human health, such claims need to be evaluated by regulatory institutes such as the European Food Safety Authority (EFSA). The EFSA Panel on Dietetic Products, Nutrition and allergies (NDA) has published their opinions regarding health claims including probiotics, most of which were rejected in the past years. Using the EFSA database, the NDA dossiers published between 2005 and 2013 were analysed to provide an overview on what grounds certain health effects were accepted as beneficial and others not. The NDA Panel distinguishes between claims that are definitely beneficial, possibly beneficial or non-beneficial to human health. Overall, 78% of all analysed health claims are considered by the NDA Panel as (possibly) beneficial to human health, in particular the gut health effects. Since, in many cases, the scientific substantiation of a particular health claim was deemed insufficient, most applications were turned down. For future health claim applications concerning probiotics to be successful, they should include specific statements on what exactly the microorganism affects, and the scientific substantiation of the particular health claim should be based on the targeted (general) population.

Keywords: beneficial to human health, European Food Safety Authority, health claim, microorganisms

1. Introduction

According to the World Health Organisation (WHO) health is defined as the 'state of complete physical, mental and social well-being and not merely the absence of disease or infirmity' (WHO, 1946). In recent years, this definition has become subject to a debate within the scientific community; it should include strategies to maintain (or improve) health. Next to the WHO, many institutions have been established on a national and international level to monitor and improve (legislation concerning) health. An example is the European Food Safety Authority (EFSA), which was established in 2002 following a series of food crises in the late 1990s. Because diet and nutrition habits significantly impact human health, the EFSA strives to improve food safety within the European Union (EU) and maintain a high level of consumer protection ('independent scientific advice on food and feed safety'; EFSA, undated). One of

the ways to achieve this goal is through evaluating health claim applications for functional foods.

According to the European Commission a health claim 'means any claim that states, suggests or implies that a relationship exists between a food category, a food, or one of its constituents and health' (EC, 2007: 8). The EFSA distinguishes three different types of health claims (described in Articles 13 and 14; EC, 2007: 11): claims attributing to growth, development and functions of the human body, both behavioural and psychological functions (Article 13-1); claims reducing the risk of disease (development) (Article 14-1a); and claims concerning children's development and health (Article 14-1b). Any health claim application made in relation to food products needs to follow guidelines as described in Regulation EC 1924/2006 (EC, 2007, 2010). One of the EFSA Panels, the Panel on Dietetic Products, Nutrition and Allergies (NDA)

evaluates the scientific substantiation of these health claim applications.

Regarding the question of defining 'health' and 'health claims', one must account for the relativity of any such definition. A psychological or physical 'improvement' for one person may be harmful to another, any particular risk reduction for one disease can be harmful when considering the course of a different disease. For instance, a reduction in platelet aggregation is beneficial for individuals with a thrombotic tendency, yet harmful for people with a tendency to bleed. Once a health claim application is submitted to the EFSA, it undergoes a number of procedures, resulting in a scientific opinion on the health claim available to the public. Such publications always contain an 'assessment' part, which consists of three separate paragraphs. In the first paragraph the food or constituent is characterised, in the second paragraph the relevance of the claimed effect to human health is reported, and in the third the scientific substantiation of the claimed effect is analysed. Each published scientific opinion includes the argumentation on whether the respective panel considers any particular statement to be a 'beneficial physiological effect' or to be 'beneficial to human health'.

A large body of clinical and experimental research has been conducted investigating the health benefits of probiotics. As many health claims focus on healthy populations, whereas most research is done in populations including patients suffering from particular diseases, it has been argued that more research should be conducted in the normal population to support claims concerning benefits for healthy subjects (Salminen and Van Loveren, 2012). What exactly is a health benefit? A question which can be answered from a physiological, philosophical and a regulatory point of view. Both applicants as well as regulatory authorities such as the EFSA need to agree on definitions and guidelines to properly evaluate health claim applications, and filter out those claims which are not considered to be beneficial to health. In this paper the regulatory point of view of a health benefit is examined by performing an analysis of the published opinions of the EFSA NDA Panel on health claim applications.

2. Methods

Firstly, online databases such as PubMed and PubMed Central were used to identify the existing scientific literature on probiotics. Secondly, a literature search was conducted using the online EFSA database (<http://www.efsa.europa.eu/en/publications/efsajournal.htm>, accessed 14 February 2013) containing all scientific opinions concerning health claim applications. Also, the 'EU Register on nutrition and health claims' was used (EC, 2013).

Publications studied

The publications used for this analysis encompass the recent publications of evaluated dossiers concerning health benefits related to probiotics. Several other health claim application dossiers that resulted in an EFSA-approval were included to provide material for comparison.

Instrumentation

The online EFSA database was searched for publications concerning possible health claims referring to probiotics using the search term 'probiotics'. However, as this search term yielded only 32 publications, it was assumed alternative terms may have been used to refer to probiotics. Therefore, the terms '*Lactobacillus*', '*Bifidobacterium*', '*Saccharomyces*', '*Streptococcus*', '*Bacillus*' and '*Enterococcus*' were also used to identify the relevant publications together with two filters, one targeting the type 'Opinion of the Scientific Committee/Scientific Panel' and the other 'Nutrition', filtering only the opinions of the EFSA NDA Panel. Each of the publications was searched in the 'relevance of the claimed effect to human health' paragraph for the key words 'beneficial physiological effect' and 'beneficial to human health'. This resulted in three different categories of statements describing definite, possible and non-beneficial effects, respectively. Papers were excluded from further analysis when they did not include either set of key words ('beneficial physiological effect' or 'beneficial to human health').

3. Results

'Probiotics' is the term used for a product containing microorganisms which (after ingestion) have a beneficial effect on the health of the host (FAO/WHO, 2001; Salminen *et al.*, 1999; Sanders, 2008; Schrezenmeir and De Vrese, 2001). In PubMed Central, an online database of peer-reviewed scientific research in biomedical and life sciences, the search term 'probiotics' gives over 3,000 scientific publications; using PubMed almost 9,000 publications can be found. In the document of the WHO and the Food and Agriculture Organization of the United Nations (FAO), experts state that health benefits can originate from consuming foods containing probiotics. Even though at that time some evidence existed pointing towards such health benefits for the otherwise healthy population, according to the authors it was still to be firmly established whether probiotic products can indeed prevent certain diseases or modulate the immune system in otherwise healthy subjects (FAO/WHO, 2001).

In Table 1, an overview is given of the number of publications found per search term. From Table 1 it is evident that a search for the major genera *Lactobacillus*,

Table 1. Overview of reports in the EFSA database for scientific opinions on health claims for probiotics.

Search term(s)	Number of publications	Number of relevant NDA reports ¹
Probiotics	32	23
<i>Lactobacillus</i>	117	37
<i>Bifidobacterium</i>	47	4
<i>Saccharomyces</i>	24	6
<i>Streptococcus</i>	31	3
<i>Bacillus</i>	9	0
<i>Enterococcus</i>	2	0

¹ Excluding the relevant NDA reports (i.e. containing scientific opinions on health claims for probiotics) that were found using a more general search term (probiotics).

Bifidobacterium, *Streptococcus*, and *Saccharomyces* yields more than twice the number of relevant publications (50) than identified by the term probiotics (23). After careful consideration, it was decided to exclude the publications

identified by the search terms '*Bacillus*' and '*Enterococcus*' from further analysis. Searching the EFSA Journal for '*Bacillus*' yielded 82 publications, but only two were from the NDA Panel; one of the papers did not mention the key words, the other was already covered by a different search term. The search for '*Enterococcus*' yielded 23 results, all published by panels other than the NDA Panel.

Below, a basic overview of all EFSA statements concerning beneficial effects is given, sorted in three different categories: definite, possible, and non-beneficial effects. A detailed summary of all individual publications containing statements on health effects can be found as Supplementary Tables S1-S7. The sorting order used by the search engine was adopted in this study. Most papers published during and after 2010 included the wording 'beneficial physiological effect', whereas most of the papers published before 2010 used the term 'beneficial to human health'. Apparently between 2009 and 2010, the EFSA NDA Panel changed its terminology for describing health claim opinions. For the purpose of this study both wordings were used to reflect the description of a health effect.

Table 2. The frequency of statements referring to a beneficial effect.

Description / summary	Frequency
Reduction of gastro-intestinal discomfort	12
Defence against pathogenic (intestinal/vaginal/etc.) microorganisms	8
Contribution to, improve or maintain (immune) defence against pathogenic (gastro-intestinal) microorganisms or pathogens/initiation appropriate immune responses	5
Improved lactose digestion for individuals with lactose maldigestion	4
Maintenance of normal blood pressure	3
Maintenance of normal blood (LDL-)cholesterol concentrations	3
Maintenance of upper respiratory tract defence against pathogens by maintaining immune defences	3
Maintenance of normal/reduction of body weight in (overweight) individuals	2
Maintenance of normal hair, nails	2
Acid neutralisation/reduction of acid production in dental plaque	2
Maintenance of tooth mineralisation/reduction of dental plaque	2
Protection of the skin from UV-induced damage	1
Normal resistance to cedar pollen allergens	1
Long-term maintenance of normal blood glucose concentrations	1
Maintenance of normal joints	1
Reduction of <i>Streptococcus mutans</i> in the oral cavity	1
Alleviation of psychological stress	1
Defence against vaginal pathogens by increasing the proportion of lactobacilli and/or decreasing the proportion of potentially pathogenic bacteria/yeasts	1
Reduction of flatulence and bloating	1
Reducing the risk of <i>Clostridium difficile</i> diarrhoea by reducing the presence of <i>C. difficile</i> toxins	1
Improvement of bowel motor function within the normal range	1
Protecting the alimentary system against pathogens	1
Reduction of tiredness and fatigue	1
Protection against heavy metals	1

Statements considered by the EFSA as beneficial to human health

In the published EFSA opinions, the claimed health effect is usually evaluated by a statement such as: The Panel considers ... to be a beneficial physiological effect; or: The Panel considers that ... is beneficial to human health. In Table 2, a description or summary of (a group of) each statement is given, together with the number of times the (group of) statement(s) was mentioned in the EFSA reports.

Statements considered by the EFSA as possibly beneficial to human health

Possible physiologically beneficial effects are usually evaluated by a statement such as: The Panel considers that ... might/may be a beneficial physiological effect; or: The Panel considers that ... might be beneficial to human health. In Table 3, a description or summary of (a group of) each statement is given, together with the number of times the (group of) statement(s) was mentioned in the EFSA reports.

Statements considered by the EFSA as non-beneficial to human health

Health claims considered not to be beneficial effects are usually described by a statement such as: The Panel considers that ... is not (in itself/considered to be) a beneficial physiological effect; or: The Panel considers that ... is not beneficial to human health. Sometimes, in the publication an explanation is given why the claim is not a beneficial physiological effect per se, but needs to be linked to a beneficial physiological or clinical outcome. In Table 4, a description or summary of (a group of) each statement is given, together with the number of times the (group of) statement(s) was mentioned in the EFSA reports.

Overall, 22% of evaluated health claim applications were made for effects to be considered non-beneficial to human health. Most of these claims were on changes in the composition of gut microbiota (Figure 1). For the other 78%, the claimed effect was considered to be beneficial or possible beneficial. In Figure 1, the health claims pertaining to gut health, immune health, and metabolic health (including obesity) are analysed separately. The data show that for gut health claims, all claimed effects were (possible) beneficial. However, these claims were not

Table 3. The frequency of statements referring to a possible beneficial effect.

Description / summary	Frequency
(Maintaining the balance of intestinal microbiota in the context of) decreasing (potentially) pathogenic (gastro-)intestinal (micro)organisms	24
Changes/improvements in bowel function/regularity (provided they do not result in diarrhoea)	7
Maintaining normal bowel function – with reduced (or maintained normal) intestinal transit, and increased bowel movements' frequency (within a normal range)	4
Normal blood concentrations of triglycerides	2
Reduction of post-prandial glycaemic responses	2
An increase in magnesium and/or calcium absorption, with consequent improved calcium/magnesium retention	1
Reducing levels of markers of inflammation (under certain circumstances)	1
Increase in satiety leading to a reduction in energy intake (if sustained)	1
Maintaining individual intestinal microbiota in subjects receiving antibiotic treatment	1
Improvement of iron absorption	1
Improving of oral health by reducing the number of <i>Streptococcus mutans</i> and by reducing the gingival and plaque indices	1
Reducing tooth demineralisation in the context of reducing the risk of caries	1

Table 4. The frequency of statements referring to a non-beneficial effect.

Description / Summary	Frequency
Increasing the number of any groups of microorganisms	21
Changes in short chain fatty acid production, or pH in the gastro-intestinal tract	4
Increasing IL-10 production by peripheral blood cells or natural killer cells (and enhancing their lytic activities)	2
Changes in / reduction of markers of inflammation (such as various interleukins)	2
Stimulation of various immunological responses	1
Reduction in numbers of circulating CD34+ cells	1

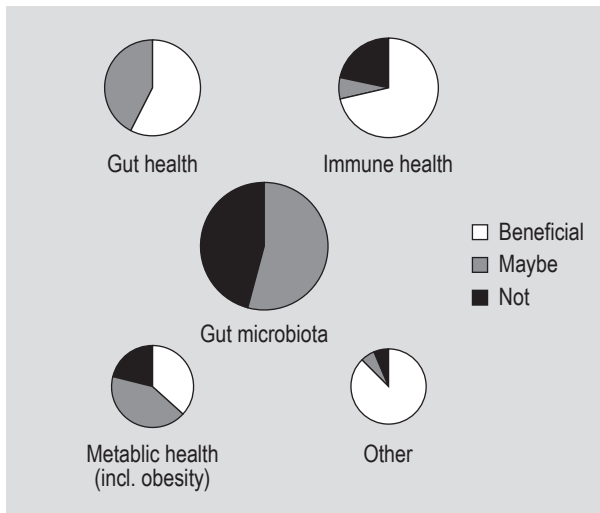


Figure 1. Outcome of EFSA NDA evaluation of claimed effects of probiotics as beneficial, possible beneficial or non-beneficial for human health. Claimed effects are grouped according to their principal domain. Metabolic health includes obesity. The size of the pies is proportional to the number of published opinions in the respective domain (gut microbiota 46, gut health 26, immune health 28, metabolic health and obesity 19 and other health effects 15).

supported by the EFSA NDA panel because of insufficient scientific substantiation.

Health claim dossiers for other food ingredients

As this analysis is limited to provide an overview on the EFSA panels' opinions regarding probiotic health claims, it should be pointed out that not every paper listed in Tables 2-4 was dealing with health claims for probiotics. While all publications selected included microorganisms, a number of studies target microorganisms already present in the human body rather than administering exogenous microorganisms (probiotics). Additionally, all but four health claim applications cited here were rejected by the EFSA. As described by Starling (2012), only 222 of all EFSA health claim applications have been approved to date. However, on the 'EU Register on nutrition and health claims' (EC, 2013), 241 applications were referred to as 'authorised'. Of these applications, 222 were health claims referring to growth, development and functions of the body (EC, 2007: Article 13-1); one 'new function' health claim (EC, 2007: Article 13-5), seven were so-called risk reduction claims (EC, 2007: Article 14-1a); and eleven were health claims concerning children's development (EC, 2007: Article 14-1b).

As most of the claims regarding probiotics were rejected, a few approved health claim applications were included for comparison (Supplementary Table S8). One of the approved claims concerns a water-soluble tomato

concentrate, with a claimed health effect related to the reduction of platelet aggregation. According to the EFSA Journal, '[t]he [NDA] Panel considers that maintaining normal platelet aggregation is beneficial to human health' (NDA, 2009a). Another claim deals with the maintenance of normal physical and cognitive functions, and maintenance of normal thermoregulation, both in relation to health claims for water. In the relevant EFSA report, it states that 'maintenance of normal physical and cognitive functions is a beneficial physiological effect' and that 'maintenance of normal thermoregulation is a beneficial physiological effect' (NDA, 2011a). Four dossiers contain health claims in relation to coronary heart disease (NDA, 2008a,b, 2009b, 2010). Each of the four health claims were based on decreased blood LDL-cholesterol concentrations, and all were considered to be beneficial to human health or a beneficial physiological effect. Moreover, in the two most recent publications, the EFSA added to its statement: 'The Panel considers that lowering blood LDL-cholesterol concentrations is beneficial to human health [or a beneficial physiological effect] by decreasing the risk of coronary heart disease' (NDA, 2009b, 2010). Using the search term 'risk' and the filter 'authorised' in the EU Register (EC, 2013), searching for dossiers containing authorised health effects, yielded seven results; besides four dossiers concerning coronary heart disease, three others referring to a health claim involving the reduction of dental plaque were found.

4. Discussion

In the scientific literature products containing probiotics have been widely established as products with a beneficial or improving effect on human health. Still, regulatory authorities, such as the EFSA, collectively express negative opinions on health claims referring to probiotics. How is this possible? Apparently, notwithstanding the body of information in this field, the specific applications for health claims were not providing sufficient evidence for that specific microorganism in the context of the claim made.

Comparing all statements found in the EFSA reports evaluating health claim applications referring to probiotics, no large irregularities or contradictions were found within and between (groups) of statements in each of the three different categories. For instance, all 24 times a decrease in pathogenic (intestinal) microorganisms was mentioned, it was evaluated as possibly beneficial to human health, never as a definitely beneficial effect, nor as non-beneficial. Interestingly, however, while the EFSA considers 'defence against' pathogenic microorganisms to be a beneficial effect, 'decreasing the number of' pathogenic microorganisms only 'may be' a beneficial health effect. Considering that 'defence against' pathogens should lead to a decrease in their numbers, it could be debated what exactly is the difference between these two health claims. The EFSA guidance on the scientific requirements for health claims related to gut

and immune function states in relation to defence against pathogens: 'Another appropriate measure for function claims related to defence against pathogens ... would be the reduction of the presence of specific pathogens ...' (NDA, 2011c).

Most apparent were statements such as 'reduction of gastro-intestinal discomfort' or 'defence against pathogenic (intestinal or vaginal) microorganisms [is a beneficial physiological effect]'; 'decreasing (potentially) pathogenic (gastro-)intestinal (micro)organisms [might be a beneficial physiological effect]'; and finally the statement 'increasing the number of any groups of microorganisms [is not considered to be a beneficial physiological effect]'. This latter opinion is remarkable, as this contrasts with the statement 'defence against vaginal pathogens by increasing the proportion of lactobacilli ... [is a beneficial physiological effect]' (NDA, 2011b). For bacterial vaginosis, the relative proportion of lactobacilli is a diagnostic criterion (Ison and Hay, 2002) and no strict criteria exist for a healthy gut microbiota.

In general, comparing statements referring to definite and possible beneficial health effects, the 'may be' and 'not-beneficial' statements were found to be more specific. Therefore, it is argued that any health claim should include general terms that are not too specific. On the other hand, some statements referred to as definite beneficial effects were found to be rather specific as well (e.g. 'normal resistance to cedar pollen allergens' as compared to 'reduction of mutans streptococci in the oral cavity' – both targeting a rather specific (group of) pollen allergens and microorganisms. Analysis of gut health and immune health effects at first suggested a discrepancy: for gut health the general term 'reducing discomfort' is considered to be a health benefit, while 'stimulating the immune system' is not. More detailed claims for gut health 'improvement of regularity' at best is a possible health effect, and 'improving the immune response against pathogens' is an approved health effect. More close evaluation however indicates that otherwise detailed statements on specific but isolated functions of the immune system (such as increased IL-10 production) are not approved as a health benefit. For a specific claim, the measurable parameters should reflect a truly beneficial effect.

It could be suggested to applicants to make their statement in a health claim application not too specific. Using the definition used by the WHO, 'health' is an ultimate state of well-being, reason for regulatory authorities to approve only those health claims which affect the general (healthy population), and thus reject all effects claiming to reduce the risk for a certain disease. As described in many opinions included in this study, unsuccessful health claim applications do include statements that are considered as beneficial, but for specific target populations only. For instance,

improved lactose digestion is described as a beneficial effect, but only for individuals with maldigestion (NDA, 2012a). With a more general definition of health including strategies to improve health, such a health claim might have been approved by the EFSA. Interestingly enough, the EFSA did approve some health claims concerning a reduction in the risk for a disease; four health claim dossiers involving coronary heart disease. Reasons could be that blood cholesterol levels are validated biomarkers for coronary heart disease. For gut health and immune health, equivalent, indisputable biomarkers need to be identified to substantiate the effect on human health.

Above arguments and considerations are reflected in one of the reports analysed in this research (NDA, 2012b). In this report, describing the effects of *Lactobacillus casei* DG CNCM I-1572, the EFSA NDA Panel explains that the 'decreasing potentially pathogenic gastro-intestinal microorganisms might be a beneficial physiological effect'. However, the scientific substantiation of the claimed effect was based on studies involving patients suffering from *Helicobacter pylori* infection treated with antibiotics. The claim targeted 'the general population (i.e. subjects without infections)' (NDA, 2012b). This is an example of a bacterial strain for which the health benefits have been proven and thus can be termed a probiotic. However, those health benefits have been demonstrated in patients rather than otherwise healthy subjects, using outcome parameters not conforming to regulatory (e.g. EFSA) criteria. Moreover, while preventing *Helicobacter* might be considered a beneficial health claim for food, treatment would be considered a medicinal claim. If the mechanism along which treatment effects are identical to preventing effects, treatment effects could be extrapolated to beneficial health effects on food. Therefore, the evident health benefit in the patient population cannot be used to substantiate a health claim. This example indicates that for regulatory purposes and for approval of health claims for probiotics more research should be conducted in the general (healthy) population. Alternatively, appropriate model populations should be identified, such as irritable bowel syndrome (IBS) patients for gastrointestinal complaints common in the general population.

To conclude, in this study a number of statements were found to be consistently used by the EFSA to indicate beneficial health effects; statements regarding both maintenance of normal or (physically) healthy physiological states and improvement or reduction of unhealthy/pathological ones. Future health claim applications advocating beneficial health effects for certain probiotics should contain specific statements indicating what exactly the microorganisms target. Additionally, the scientific substantiation of the particular health claim should be based on the target population. Finally, it must be emphasised that this analysis is restricted to the statements reported in the

EFSA dossiers dealing with probiotics. The extent to which these results can be extrapolated to other EFSA opinions is, therefore, limited. Whether health effects that have not been used in health claim applications (e.g. longevity) could be acceptable, cannot be predicted. The methodology used in this paper for probiotics could also be used for the analysis of other functional food categories such as prebiotics and antioxidants.

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Supplementary material

Supplementary material may be found online at <http://dx.doi.org/10.3920/BM2013.0019>.

Table S1. Results search 'probiotics'.

Table S2. Results search '*Lactobacillus*'.

Table S3. Results search '*Bifidobacterium*'.

Table S4. Results search '*Saccharomyces*'.

Table S5. Results search '*Streptococcus*'.

Table S6. Results search '*Bacillus*'.

Table S7. Results search '*Enterococcus*'.

Table S8. Detailed overview approved health claim dossiers.

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