

# Probiotics for the Healthy Consumer: An Overview

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Probiotic uses encompass a continuum of regulatory classifications, including foods, drugs, dietary supplements, and medical foods. But foods, including dietary supplements, are currently the primary product category for probiotics, especially in the United States and the European Union. Whereas drugs are often targeted toward people with disease, foods are for the general population. Evidence for probiotic benefits includes many drug uses. But probiotics have the potential to benefit healthy people as well. Probiotics may reduce the risk of healthy or at-risk people getting sick. For example, some probiotics have been shown to reduce the risk of atopic eczema in infants and the risk of common infectious diseases and may reduce the risk of cardiovascular disease through lowering density blood lipids. Some probiotics may also improve digestive function by normalizing gut transit, improve lactose digestion for lactose-intolerant individuals, and help manage symptoms associated with antibiotic use or functional bowel disorders. New avenues of research suggest a possible role of gut microbiota in conditions such as obesity and mental function; probiotic interventions are being researched for these applications. This article provides an overview of the use of probiotics in health in the context of efficacy, safety, and regulatory considerations.

**Key words:** *delivery matrix, probiotic, regulatory, safety*

Consumers often wonder if probiotics are something that can be of benefit to healthy people or are useful only for people suffering from gastrointestinal disease, such as infectious diarrhea or inflammatory bowel disease. Evidence that healthy people can benefit from probiotics, either through reduction of risk of certain diseases or through dietary management of some digestive conditions, is building and is addressed by several leading experts in this issue of *Functional Food Reviews*. This article provides an overview of the use of probiotics—delivered in foods, including dietary supplements—to promote health, not treat disease. Efficacy, safety, and regulatory considerations are discussed.

## Probiotics for the Healthy Consumer

People's physical states can range over a spectrum from healthy to having a disease. They may have no health issues, have no current health issues but at elevated risk for developing a disease, have health complaints that do not reach the severity of disease diagnosis, or have a diagnosed disease. Although most people, with or without diagnosed

disease, can benefit from health-promoting lifestyle choices, people without a diagnosed disease have an opportunity to improve their likelihood of staying disease-free. Furthermore, all people, regardless of where they sit on this health-disease spectrum, have a chance of acquiring an acute illness, such as a cold, influenza, or a gastrointestinal infection. In this realm, dietary choices, including probiotics, may provide a compelling approach to reduce the likelihood of getting sick or manage health complaints. In the United States, probiotics are mostly sold as nutritional products, either foods or dietary supplements. As such, they are products targeted toward the general population and are used to reduce the risk of disease or enhance or maintain normal bodily function. (Products intended to cure, treat, prevent, or mitigate disease fall exclusively in the drug category in the United States.) Herein lies the value of probiotics for the healthy consumer. Table 1 lists probiotic uses for enhancing or maintaining health. The magnitude of effect or strength of evidence for the indicated probiotic effects varies among end points, probiotic strains, and study population. (See the articles by Guarner and colleagues and Floch and colleagues for evidence-based assessment of different probiotic effects.<sup>1,2</sup>) Where available, I have indicated systematic reviews or meta-analyses that can be consulted for such information. In most cases, although combined evidence suggests positive, probiotic benefit, additional research is deemed necessary. I have included management

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of obesity, insulin resistance, and some mental functions in this table because these are important concerns to healthy people. However, these end points are only experimental at this point, and there are few to no human data. These end points point to exciting new avenues of research, which stem from the broad range of physiologic effects associated with our colonizing microbiota.

Although a very clear divide exists between probiotic uses for drugs (to cure, treat, and prevent disease) and

foods (for the general population) in the United States and European Union (EU), Canada has defined its regulatory categories differently. Health Canada regulates a category of product called “natural health products,” which are naturally occurring substances that are used to restore or maintain good health and must be licensed for use.<sup>3</sup> This category allows use of natural health products for the prevention or treatment of an illness or condition, the reduction of health risks, or the maintenance of good

**Table 1.** Probiotic Uses for Enhancing or Maintaining Health

<i>Use</i>	<i>Target Consumer</i>	<i>Comments</i>	<i>Reference*</i>
Reduce risk of atopic eczema in infants	Healthy but at-risk infants or pregnant mother	Benefit does not extend to other forms of allergy	23
Reduce the risk of common infectious diseases; reduce absences from day care, school, or work	Healthy children or adults	Common infectious diseases include acute respiratory tract infections such as colds or flu-like symptoms, and gastrointestinal infections	24–28
Manage symptoms of functional bowel symptoms; improve minor digestive upsets	People with mild to moderate functional bowel symptoms or IBS; healthy people with minor digestive upset complaints	Given that IBS is a syndrome and not a disease, that symptoms exist across a spectrum of severity, and that the symptoms occur in a wide number of people, people with mild to moderate symptoms are considered here to be part of the general population. <sup>22</sup> Target minor digestive upsets include gas, bloating, occasional constipation, occasional diarrhea, and others.	29–31
Improved lactose digestion	Healthy people with lactose intolerance	Lactose intolerance includes symptoms associated with inability to digest lactose	32
Management of symptoms associated with antibiotic use	People on antibiotics but with healthy gut function prior to antibiotic use	The impact of antibiotics on the gut in many cases reflects the response of a healthy gut to the perturbation caused by the antibiotic. In cases where the gut is healthy when the antibiotic is administered, the prevention of antibiotic-associated diarrhea is considered a response of a healthy subject.	33, 34
Management of colic in infants	Healthy infants		35
Reduce low-density blood lipids	People with hypercholesterolemia		36, 37
Management of obesity or insulin resistance	Healthy people at risk for developing diabetes or obesity	Experimental stages to date. The potential role of gut microbiota to impact development of obesity or insulin resistance is a new investigational opportunity for probiotic interventions. Human data are forthcoming.	38, 39
Mental functions, such as pain sensation, depression, anxiety, stress	Healthy people	Experimental stages to date. The potential role of gut microbiota to impact psychological disorders is a new investigational opportunity for probiotic interventions. Human data are forthcoming.	40–43

IBS = irritable bowel syndrome.

\*Meta-analyses or systematic reviews if available are cited rather than primary research citation. See references for indications of magnitudes of effects and strength of evidence.

health. In the probiotic category, for example, BioK+100<sup>4</sup> (containing *Lactobacillus casei* LBC80R and *Lactobacillus acidophilus* CLI285) is approved for prevention of *Clostridium difficile* infection in hospitalized patients, and Align<sup>5</sup> (containing *Bifidobacterium longum* subsp. *infantis* 35624) and TuZen<sup>6</sup> (containing *Lactobacillus plantarum* 299V) were approved for irritable bowel syndrome symptoms. Such uses would not be allowed by the Food and Drug Administration (FDA) on probiotic foods or dietary supplements in the United States. Canada's regulatory approach is instructive and worthwhile for the probiotic category.

### Use of Probiotics for Healthy Consumers: Regulatory Constraints

In recent years, the probiotic field has confronted significant regulatory obstacles for the use of probiotics in healthy consumers. Probiotic claims, safety, and the conduct of research on probiotics have all been significantly impacted by regulatory actions, especially in the United States and EU. The importance of these regulatory matters in current times is reflected in some recent articles.<sup>7-11</sup>

#### Probiotic Product Claims

In the case of probiotics, regulators in the EU have not been convinced that the evidence is sufficient to adequately substantiate any probiotic benefit so far submitted to them. With the exception of yogurt cultures improving lactose digestion in lactose-intolerant people, no probiotic claims have been approved. There are many confounding factors contributing to this state of affairs: lack of a clear direction on what research is required,<sup>7,11</sup> exclusion of well-conducted studies because patient (not healthy) populations or disease outcomes were studied, difficulty in defining physiologic benefits with healthy study subjects, and the existence of studies that do not substantiate the physiologic benefit (ie, null studies). Some believe that the standard of evidence required by EU authorities is unrealistic for foods. However, as regulatory expectations become clearer and as assessors become more knowledgeable, specific probiotic claims are likely to be approved in the EU. Nonetheless, until this time, even use of the word *probiotic* is restricted on food products in the EU. A probiotic is a live microorganism that, when administered in adequate amounts, confers a health benefit on the host.<sup>12,13</sup> If you accept this definition of a probiotic, then the logical conclusion is that if a health

benefit has not been established, use of the term *probiotic* is not appropriate. The question remains if evidence is suitably compelling that the soft claim of "probiotic" could be justified based on the large body of existing scientific evidence. There is little doubt about the physiologic effects of some probiotics. But the conduct of appropriately designed studies and the generation of consistent evidence for specific effects that will be suitably convincing to regulators must be developed before specific claims will be approved.

Unlike the EU, in the United States, certain types of claims can be made on foods without regulatory approval. Structure or function claims, which relate the food to the normal structure or function of the healthy human body, do not need approval, but they do need to be scientifically supported. (Claims that relate a food to the reduction of risk of disease can also be made in the United States, but only with approval.) In some cases, companies may try to adapt evidence generated on patient populations to support claims on healthy populations. For example, a company may judge evidence that a probiotic strain can reduce the incidence of antibiotic-associated diarrhea as substantiating a claim of "supports a healthy digestive tract." This claim is an appropriately worded structure or function claim, but regulators may challenge the validity of such evidence to substantiate a claim on a food or supplement. Furthermore, this claim tells the consumer or health care provider little about the science behind the product.

Determining how to design studies suitable to substantiate health benefit claims on a food is a challenge for food companies. In addition to the scientific challenges of such research, studies must comply with regulatory expectations, which are not always clearly stated and which can differ among different countries. Regulators may even prevent the conduct of research on foods or supplements if they interpret the study as a drug study.

#### Research

In the United States, researchers have special difficulty with launching studies on probiotic foods. Because probiotics are live microbes, the FDA generally considers them to be under the jurisdiction of the FDA's Center for Biologics Evaluation and Research (CBER). CBER's role is to evaluate biologic drugs, and when it evaluates probiotic research, it seems to automatically conclude it is drug research. Drugs, according to US law, are substances that cure, treat, prevent, or mitigate disease or (with the exception of foods) affect the structure or function of the

human body. Impacting the structure or function of the human body, or reducing the risk of disease, is within the purview of both drugs and foods. However, CBER's very broad view of what constitutes a drug study leads it to require Investigational New Drug (IND) applications for most human studies on probiotics.

This becomes a problem if the intention of the study sponsor's is not to investigate a drug. If research is intended to substantiate claims on a food (or dietary supplement), then an IND application is an expensive, time-consuming, unnecessary task that may force the product into the drug category. Furthermore, it sets into motion requirements for safety studies that may not be required for a food. Institutional Review Boards (IRBs) are loathe to challenge the FDA, so even if an IRB considered a study to be safe, it may not allow the study to proceed without an IND application. Another consequence of this approach is that independent investigators (ie, not company sponsored) are precluded from conducting human trials on probiotic foods or dietary supplements. If they are required to conduct such studies under an IND application, they would need full cooperation from the product manufacturer to meet the IND information requirements. Such restrictions on probiotic research would be understandable if consumer protection was the goal, but such restrictions have been imposed on studies conducted with probiotics currently being marketed to healthy subjects and on studies approved by IRBs. A valuable legal perspective on this issue is available from Degnan, which offers suggestions for when INDs should, and should not, be required for probiotic research.<sup>14</sup> The case is presented that not all human research involving probiotics falls under the IND rubric. A probiotic can fall along a continuum of regulatory classifications (food, drug, dietary supplement, medical food); regulators should recognize that probiotics are not automatically drugs.<sup>15</sup>

Because of this restrictive regulatory situation on human studies with probiotics in the United States, companies are turning to non-US locations for conducting probiotic food research. The upshot of this regulatory positioning is that probiotic drug development in the United States is alive and well. But human research on probiotic foods—and the researchers who want to study them—will suffer.

### Safety

Probiotic safety for use in foods can be assessed through both the history of safe use and scientific testing. Strains from two genera, *Lactobacillus* and *Bifidobacterium*, are

widely used as probiotics. These two genera occur as normal constituents in a variety of fermented foods worldwide and as normal commensals of the human microbiota. Other genera, species, and strains are also used, or proposed for use, as probiotics, and some of these do not enjoy a long history of safe use in foods. Furthermore, safety for use in foods targeted toward the generally healthy population should not be interpreted to mean that even a Generally Recognized as Safe (GRAS) probiotic is safe for populations with serious underlying health issues.

Therefore, it is necessary that any researcher or commercial entity proposing to use a new strain as a probiotic for humans carefully assess whether the proposed use for the new strain meets the safety standards for such use. Sanders and colleagues recently summarized key considerations for establishing the safety of a microbe for probiotic use.<sup>16</sup> Hempel and colleagues, in a report on the safety of probiotics to prevent or treat disease, concluded that safety questions are not adequately addressed in the published literature database of clinical studies.<sup>17</sup> In the EU, the safety assessment approach is Qualified Presumption of Safety (QPS), which provides a list of species that are presumed safe and can be used in foods with no further safety assessment, except documentation of the lack of transferrable antibiotic resistance genes.<sup>18</sup> In the United States, safety of food ingredients can be assessed through a GRAS determination. If they so choose, companies can submit these determinations to the FDA for comment. Table 2 shows the strains for which GRAS notifications have been filed and the FDA had no comments. (The FDA does not “approve” these notices; it only indicates if it considers there to be shortcomings in the notice or flaws in the conclusions.) Note that this list is short and is very different from the QPS system in several regards. First, there is no general GRAS list of probiotics that are considered safe. All of these GRAS notices were compiled for specific strains being used for a specific use in foods. The QPS system lists species (not strains) that it considers acceptable for use in food. Second, a GRAS notice is for an intended use. A GRAS notice is not a blanket acceptance of any conceivable food use; it is for a specific food use and dose, and an important component of the GRAS notice is that safety is documented for the expected consumption levels in the particular food application. The assessment is conducted by recognized experts in the field.

One major component to establishing probiotic safety is accurate identification and characterization of the probiotic strain. For many experts in the safety arena,



**Table 2.** Probiotic Strains for Which GRAS Notifications Have Been Filed and FDA Had No Comments

Strain	Intended Use	Date of FDA Response
<i>Bifidobacterium longum</i> strain BB536	Ingredient in miscellaneous foods at a maximum level of $1 \times 10^{10}$ cfu/serving and in milk-based powdered infant formula at a level of $1 \times 10^{10}$ cfu/g of infant formula powder that is intended for consumption for term infants aged 9 mo and older	July 8, 2009 GRAS Notice 000268
<i>Lactobacillus casei</i> subsp. <i>rhamnosus</i> strain GG	Ingredient in term infant formula at levels not to exceed $10^8$ cfu/g of powdered formula	May 29, 2008 GRAS Notice 000231
<i>Lactobacillus reuteri</i> strain DSM 17938	Ingredient in miscellaneous foods, drinks, and chewing gum at a level up to $10^9$ cfu/serving and in a drinking straw at a level of $10^9$ cfu/straw	November 18, 2008 GRAS Notice 000410
<i>Bifidobacterium lactis</i> Bb12 + <i>Streptococcus thermophilus</i> Th4	Ingredients in milk-based infant formula that is intended for consumption by infants 4 mo and older, at levels not to exceed good manufacturing practice	March 2, 2002 GRAS Notice 000049 Additional correspondence regarding tetracycline resistance gene ( <i>tetW</i> ) later found in chromosome: November 28, 2005
<i>Lactobacillus rhamnosus</i> HN001	Ingredient in milk-based powdered term infant formula that is intended for consumption from the time of birth, as well as in milk-based powdered follow-on formula, at a level of $10^8$ cfu/g of the formula powder	August 31, 2009 GRAS Notice 000288
<i>Bifidobacterium animalis</i> subsp. <i>lactis</i> Bf-6	Ingredient for miscellaneous foods, drinks, chewing gum, and water at a maximum level of $10^{11}$ cfu/serving	September 29, 2011 GRAS Notice 000377
<i>Bacillus coagulans</i> GBI-30, 6086 spores	Ingredient in miscellaneous foods at a maximum level of approximately $2 \times 10^9$ cfu/serving but not intended for use in any product that would require additional review by the US Department of Agriculture	July 31, 2012 GRAS Notice 000399
<i>Lactobacillus casei</i> strain Shirota	Ingredient in fermented dairy products at a maximum level of $4 \times 10^8$ cfu/mL	December 10, 2012 GRAS Notice 00429

Adapted from Food and Drug Administration. Available at: <http://www.accessdata.fda.gov/scripts/fcn/fcnNavigation.cfm?rpt=grasListing> (accessed March 8, 2013).

FDA = Food and Drug Administration; GRAS = Generally Recognized as Safe.

total genomic sequencing and analysis are considered essential to provide confidence that no genes of concern are harbored by the strain. Inadequate characterization has been a major reason for rejection of probiotic health claims in the EU.

### Probiotics in Food: How Important Is the Food Matrix?

A probiotic product needs to deliver adequate viable probiotics to the site of action in the host. This may be to the oral cavity for a probiotic targeting halitosis or cariogenic bacteria, to the colon for a probiotic targeting colonic transit, or to the vaginal tract for a probiotic targeting recurrent bacterial vaginosis. Once the probiotic reaches the site of action, it needs to be able to perform required functions to confer the intended health benefit.

The variables encountered by the probiotic when executing these functions are many, and, conceivably, the type of food delivering the probiotic might impact probiotic efficacy.

Probiotics are available in a variety of foods and dietary supplement formats. Does the same probiotic delivered in a yogurt, a chocolate bar, or a capsule, for example, function any differently? The following could in theory be impacted by the delivery matrix: the viability of the probiotic in the product; the ability of the probiotic to survive in vivo to the needed site of action; functional activities of additional components in the delivery matrix (eg, prebiotics, fiber); probiotic physiology related to the specific health benefit (e.g., ability to produce bacteriocins or antiinflammatory cytokines); host physiology; or colonizing microbiota.<sup>19,20</sup> What is not known, however, is the relative importance of any matrix-specific changes on the overall ability of a probiotic to confer the intended

health benefit. It is reasonable to conclude that if a food matrix reduces probiotic survival in the product, then a concomitant reduction in probiotic benefit could be expected. But delivery matrix changes that do not impact probiotic survival could still result in detectable changes in probiotic physiology, as measured, for example, by altered gene expression patterns.

What is needed is an approach for judging, with reasonable (not 100%) certainty, when such changes might be accompanied by reductions in probiotic efficacy. Shifts due to changes in the delivery matrix may be dwarfed by factors such as differences in host genetics among different consumers, the variability of the host diet, the age of the consumer, or host microbiota, none of which are controlled within the context of consumption of a functional food. This must be taken into consideration when considering a requirement to reconduct clinical trials to substantiate efficacy in a new food matrix.

The challenge, therefore, is to develop a means to establish “functional equivalency.” The fundamental question is at what point do matrix alterations change the expected profiles of safety and efficacy for a probiotic strain? Given that it would be impossible to repeat safety and efficacy assessments for every minor change in conditions, what is a reasonable approach? It is noteworthy that in both the EU and the United States, official positions suggest that a changed delivery matrix may be viewed as equivalent to a changed substance. In the United States, the FDA issued a draft guidance document on when a New Dietary Ingredient (NDI) notification—a document outlining the rationale that a dietary supplement is safe for its intended use—is necessary for an ingredient used in a dietary supplement.<sup>21</sup> This guidance states that changes in fermentation conditions may constitute “chemical alteration,” which can trigger the need for a new NDI notification filing. This guidance has not been finalized, so the ultimate position of the FDA on this matter is not yet established. In the EU, the scientific committee evaluating petitions for health claims on foods has indicated that studies on probiotic foods should be conducted using the food or formulation being marketed<sup>22</sup> because it cannot be guaranteed a priori that a different food format would have the same functionality. Input from the scientific community on a reasonable, science-based approach to managing this issue is required.

A much-needed advance in this field is the development of preclinical tests that could give an indication that physiologic activity has not substantively changed when new conditions are imposed. In the absence of such validated, predictive tests, reconducting clinical trials may

be deemed necessary. Testing survival of the probiotic through gut transit in humans or in vitro gut models is an important first step. Changes in probiotic survival would trigger concern, but it is also conceivable that physiologic functions that dictate survival could be maintained when functions that dictate the health benefit are not. A more robust approach would test the specific benefit being claimed, relying on an established mechanism of action. For example, tracking immune function markers in animal models for probiotics being used for their immune effect, or bacteriocin production in animal models for probiotics being used for specific antipathogen activity, would provide a measure of assurance that the biologic activity of the probiotic is retained. Transcriptome and metabolic analyses might provide a more global picture of the physiologic status of the probiotic. This problem is one of the most critical issues facing commercialization of probiotics today. Clearly, guidance is needed to avoid costly clinical trials if they are unnecessary.

## Conclusions

The use of probiotics for healthy consumers shows promise. Given that probiotics are so often used in products targeted toward the general population (ie, foods and dietary supplements), research further documenting such effects in the general population is important. Regulatory positions on probiotic claims and research discourage the probiotic category, but I am optimistic that the potential applications of probiotics emerging from the bounty of new information on the importance of the colonizing microbiota to human health will propel the field forward.

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