

## Review

# Safety Aspects and Implications of Regulation of Probiotic Bacteria in Food and Food Supplements

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### ABSTRACT

The application of living bacteria as probiotics in food or food supplements requires a careful safety assessment. This review summarizes key issues concerning the safety aspects of bacteria added to particular products marketed for improvement of general health or treatment of (post)infectious symptoms. The bacteria used in such products should be completely safe; however, it can be challenging to provide evidence for absence of all virulence properties. In some cases, virulence factors have been detected in probiotic bacterial strains, and the implications of these traits for safety assessments are discussed. Horizontal gene transfer can result in acquisition of virulence genes or antimicrobial resistance in probiotic bacteria. Antimicrobial resistance in these bacteria can possibly aid the spread of undesired resistance in intestinal bacterial populations. The relative risk of such gene transfers is considered. The generation of complete bacterial genome sequences can both resolve and create safety issues. Current practices of safety assessment procedures in the United States and the European Union are briefly reviewed and a future outlook is provided.

Bacteria deliberately added to food products are used either as technological additives (starter or protection cultures) or as functional additives for human health benefits. An increasing number of commercial products (food and food supplements) containing viable bacteria are marketed for their beneficial effect on the immune system or on human health in general. Starter or protection cultures are added for technological purposes and are not considered in this study. Various terms (e.g., probiotics, synbiotics, and functional food) and definitions are in use for such products. Gibson and Roberfroid (30) defined probiotics as “microbial food supplements that beneficially affect the host by improving its intestinal microbial balance.” Six years later, experts consulted by the World Health Organization and the Food and Agriculture Organization (26) refined this definition as “live microorganisms which when administered in adequate amounts confer a health benefit on the host.” We suggest the following slightly modified definition of probiotics: “food or food supplements containing defined microorganisms in sufficient numbers to reach the gut in viable status resulting in positive health effects after consumption.” This definition does not contradict international and scientific definitions but adds both qualitative (defined microorganisms) and quantitative (sufficient numbers) requirements to the presumed positive health effect.

Probiotic agents are used for prevention of enteric diseases and intestinal microbial imbalance or as treatment for these conditions. Described health benefits of probiotics

have been extensively reviewed elsewhere (18, 31, 35, 39, 40). These benefits include prevention and treatment of acute gastrointestinal infections (notably in children), treatment of antibiotic-associated and *Clostridium difficile*-associated diarrhea, and reduction of symptoms in cases of inflammatory bowel disease (18, 41, 48) among more far-reaching claims such as prevention or treatment of colon cancer (31). Reduction of diarrhea in lactose-intolerant individuals also has been described (46). Other suggested benefits are enhancement of the immune system (42), synthesis of nutrients in the gut, and decrease in the prevalence of allergies (39). Young children are specific target groups for probiotics (31, 44, 56). The effectiveness of probiotics is not the subject of this review. Instead, we address the safety aspects of products containing purposefully added viable bacteria.

Probiotics are commonly (though not exclusively) based on fermented milk products, e.g., yogurt and yogurt products, in which the fermenting microorganisms are viable at the time of consumption, although consumers are not always aware of this fact (34). Examples of products and the bacterial species they contain are given in Table 1. The marketing of fermented dairy products is rapidly expanding in the United States and Europe; in Europe, probiotics currently represent up to 20% of such products (15). In addition to their use in human foods, probiotics are used in animal foods to enhance and stabilize the growth of fattening animals (51). Probiotics are commonly used as replacements for antibiotic growth-promoting feed additives, especially because the use of such additives is now banned

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