Prebiotics: Scientific criteria and regulatory considerations

Introduction

The lack of a harmonized EU framework for prebiotics creates regulatory uncertainty for food and supplement manufacturers, making it difficult to make claims at both EU and national levels. While some prebiotics have approved health claims, broader use of the term remains restricted under Regulation (EC) No 1924/2006. The term "prebiotic" is considered an implied health claim and may only be used if accompanied by an authorized specific claim—a position upheld by the European Commission (EC) and most Member States (MSs). In contrast, countries like Canada and Japan allow function claims, while the USA allows structure/function claims, offering greater flexibility and clearer market advantages.

Despite evidence that prebiotics support beneficial microorganisms, the European Food Safety Authority (EFSA) does not consider this alone sufficient to demonstrate a direct health benefit to the host, and requires proof of a direct, measurable health benefit, beyond microbiota modulation. In the absence of clear, harmonized criteria, this regulatory ambiguity will continue to hinder innovation, market access, and consumer understanding, leaving the EU at a global disadvantage[i].

i. Member States like Italy, Czech Republic and the Netherlands, have issued national guidance on the use of the term "prebiotic". As a result, products that may be considered compliant in one Member State may face restrictions in another.

Objective of the document

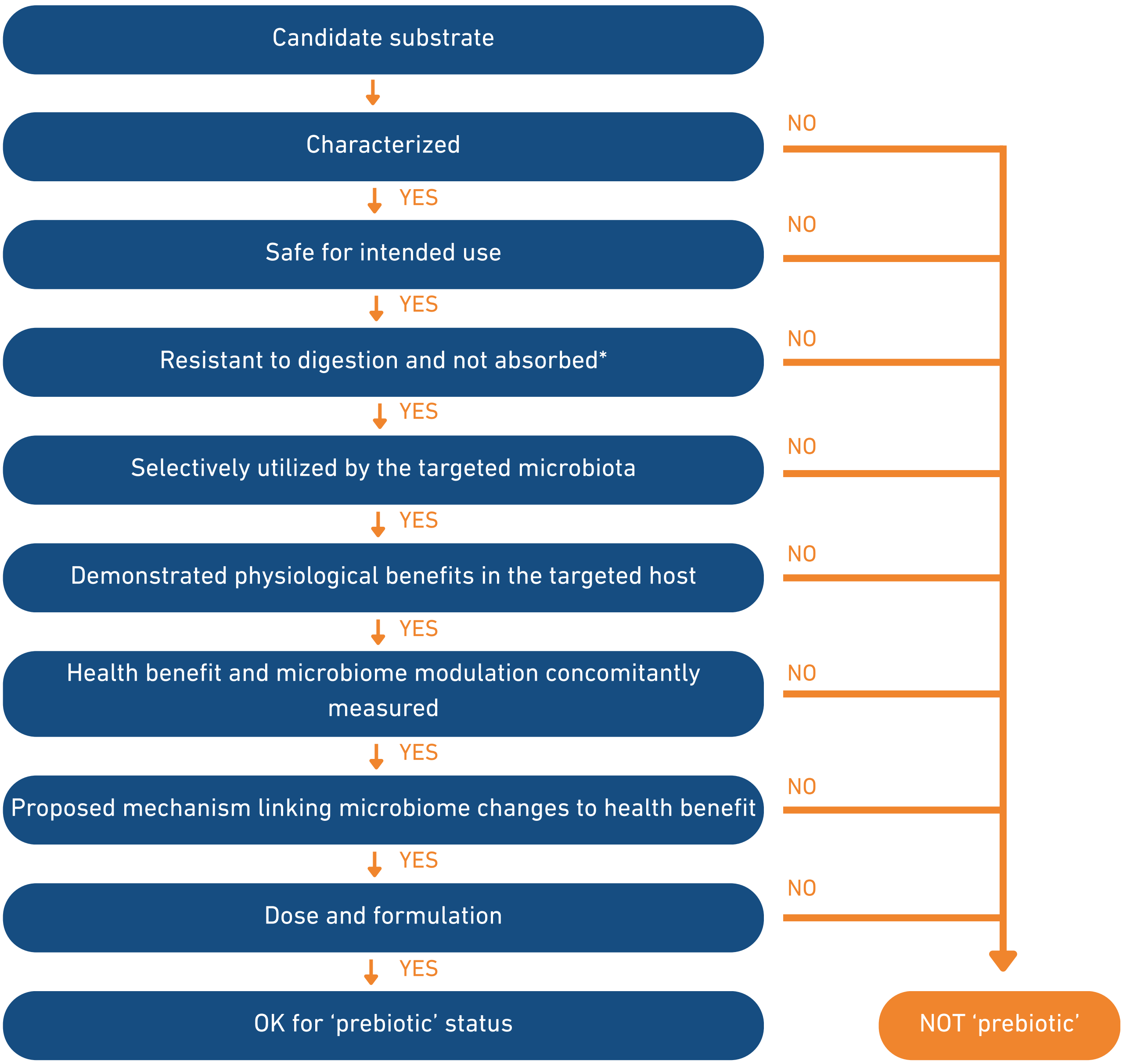
Since its introduction in 1995, the term 'prebiotic' has evolved, with the definition proposed by the International Scientific Association for Probiotics and Prebiotics (ISAPP) 'a substrate that is selectively utilized by host microorganisms conferring a health benefit' now representing the broadest scientific consensus at the global level[1].

EU Specialty Food Ingredients fully supports and endorses this definition.

The objective of this paper is to clarify the different criteria included in ISAPP definition for identifying prebiotics, in order to support stakeholders' negotiations with MSs national Authorities and stakeholders. This effort is substantiated by the existing scientific literature, including key publications from the ISAPP, the International Life Sciences Institute (ILSI), and the International Probiotics Association (IPA).

Criteria to fulfill

In line with ISAPP requirements[2,3] and EFSA guidelines[4], a well-substantiated health benefit of prebiotics requires at least one clinical study conducted according to generally accepted scientific standards, demonstrating concomitantly a selective utilization as measured by microbiota modulation (composition and/or function) and the associated health benefit[5]. In addition, the supportive array of evidence must demonstrate a beneficial effect at an applicable dose in a food product or supplement and must be convincing. It must also support a plausible mode of action on health by clear scientific rationale and sufficiently robust data, with no substantial contradictions across studies. To ensure reliability, standardized protocols, validated biomarkers, and advanced data integration and analysis tools are also necessary.



* Only relevant for prebiotics targeting gut microbiota.

Figure 1: Decision tree for classifying a substance as a prebiotic targeting the gut microbiota, based on the ISAPP checklist[3].

Characterized substrate

In the EU, health claims require authorization by the EC following scientific evaluation by EFSA. A critical part of this process is thorough characterization of the food or ingredient, including source, composition, physical and chemical properties, and batch variability, supported by scientifically sound and standardized analytical methods[4].

According to ISAPP, the proportion of prebiotic content in the final product is crucial, along with identifying other components and understanding the source and production process. Prebiotics must be produced under Good Manufacturing Practices (GMP), as manufacturing methods can affect their structure and function[2,6].

Prebiotics structure and composition may vary greatly, influencing their digestibility and microbial use. Key characterization parameters include degree of polymerization, linkage types and may be complemented by monomer composition, ratio of each glycosidic linkage or branching structure. Identification, characterization and disclosing proportion of both active and other components identified in the final ingredient may be valuable for understanding prebiotic impact[2]. For the claim to be valid, the prebiotic substance must remain stable and retain its functional properties throughout processing, storage, and preparation[2,4].

Safe for intended use

Prebiotics must be safe for its intended use and, in case of a novel food, undergo pre-market authorization.

The specific parameters to be evaluated may vary by intended product category (e.g. foods, supplements, food for special medical purposes) and target population (e.g. infants, vulnerable groups).

Resistant to digestion and absorption

A prebiotic is defined as "a substrate that is selectively utilized by host microorganisms conferring a health benefit"[1]. Dietary prebiotics remain the most studied and must resist digestion to reach the colon intact[1,6].

This resistance includes survival through gastric acidity, enzymatic hydrolysis, and absorption in the small intestine[1,6]. Foundational physiology is a key initial step to better understand metabolic fate of the ingredient. The small intestine, the main site for nutrient digestion and absorption, uses various enzymes and specialized epithelial cells to break down food and transport nutrients via passive, active, or facilitated mechanisms. Compounds like monosugars, amino acids, and fatty acids are thus excluded from the prebiotic definition, as they are absorbed before reaching the colon[6].

Selectively utilized by the targeted microbiota

Prebiotics must be selectively utilized by host microorganisms, demonstrated by statistically significant changes in microbial composition or function in at least one well-conducted human clinical trial, considering the totality of evidence[1,4]. These changes may be narrow or broad but must not affect the entire microbiota and should be linked to health-relevant metabolites[6].

ISAPP clarifies that selectivity can involve shifts in one or more taxa or microbial activity, provided the affected microbes and their metabolites are associated with health benefits[1]. Selectivity must be shown versus appropriate control, and both microbial and clinical outcomes are required in the same study to establish prebiotic status[2,4].

Definition of a prebiotic substance vs fermentable fiber

In the ISAPP 2017 consensus statement on the definition and scope of prebiotics, prebiotics are defined as substrates that are selectively utilized by host microorganisms and confer a demonstrated health benefit. Selectivity does not imply action on only a single microbial group; rather, a prebiotic may be utilized by several beneficial microbial groups, but not broadly by the entire microbiota. In addition to selective utilization, a prebiotic substance must result in a net health benefit, with the microorganisms stimulated and the metabolites produced being linked to a clearly defined beneficial health outcome. By contrast, fermentable dietary fibres are generally metabolized by a wide range of microorganisms and do not, by definition, require selectivity or a documented, targeted health effect.

Demonstrated physiological benefits in the targeted host

Clinical substantiation of a prebiotic claim

To be defined as a prebiotic, an ingredient must be supported by robust clinical substantiation. This includes at least one randomized, controlled, blinded clinical trial conducted on the target population, with precisely defined inclusion criteria. The study must demonstrate both selective modulation of the gut microbiota and associated health benefits within the same trial. Furthermore, the ingredient must be tested at a dose that is applicable to real-world food formulations—meaning it can be reasonably consumed within a single day to achieve the claimed health effects[2,4].

Digestive Health

Prebiotics support digestive health through microbiome-mediated mechanisms, initiated by selective fermentation of beneficial gut microorganisms. Bacterial growth increases fecal bulk, lowering transit time. Short-chain fatty acids (SCFAs) acidify colonic content and stimulate peristalsis, while prebiotics also bind water to soften stools[7]. These shifts are linked to improved bowel function, with bowel regularity among the most substantiated effects[8,9]. Prebiotics also enhance nutrient and mineral absorption, especially calcium and magnesium, through fermentation-induced pH changes and SCFA production, improving solubility and bioavailability[10,11]. Increased calcium absorption supports bone mineral density and development, crucial in early life[12]. According to EFSA, digestive health claims must demonstrate physiological benefits for the host, such as normal bowel function, reduced GI discomfort, or improved absorption.

Validated outcomes include increased stool frequency, decreased stool consistency, reduced transit time, and increased fecal bulk[13]. Altogether, human trials consistently show prebiotics' digestive benefits, linked to specific microbiota changes.

Metabolic health: overweight and obesity, insulin sensitivity, cardiometabolic risk factors

Gut microbiota and its fermentation metabolites, such as SCFAs, are key drivers of prebiotic health benefits, particularly linked with metabolic health of the host[14,15].

Results from clinical studies indicate that prebiotics consumption may:

- Improve glycemic control and insulin sensitivity both in healthy adults and in subjects suffering from obesity or type 2 diabetes[16,17,18];
- Induce satietogenic effects by impacting the release of appetite-regulating hormones[16,18,19];
- Support body weight management and attenuate body fat mass and weight gain[16,18,20];
- Contribute to manage dyslipidemia, via reduction of triglyceride and LDL cholesterol levels, associated with obesity and cardiometabolic risk[16,18].

EFSA's 2012 guidance sets specific requirements for measuring endpoints related to weight loss and management as well as for metabolic and cardiovascular health. These outcomes must be assessed using validated methods, and any claimed effect must be demonstrably beneficial to human health.

Immune health: defense against pathogens, allergen hypersensitivity

A well-functioning immune system is vital for defense against pathogens and allergens. Prebiotics may support immune health by modulating the gut microbiota, which produce SCFAs that influence immune responses locally and systemically. They may also interact directly with immune cells in the gut via carbohydrate receptors, potentially triggering immune effects[6]. Clinical studies suggest potential benefits, particularly in populations at risk of immune suppression (e.g., elderly, stressed individuals), including improved vaccine responses and reduced infection rates. However, many studies report changes in immune markers (e.g., lymphocyte counts, cytokines, microbiota composition) without linking them to tangible health outcomes[7,21].

EFSA recognizes immune health claims in two categories: protection against infections and improved response to allergens. Claims must be supported by well-controlled human studies showing clinical benefits, such as reduced incidence or severity of symptoms. Mechanistic data may support a claim but cannot substantiate it alone[4]. To date, only vaccination studies showing increased antibody levels beyond a protective threshold have been accepted. No EU-approved health claim for prebiotics and immune health exists, due to lack of validated biomarkers and insufficient evidence[7].

Cognitive health: mood, anxiety or psychological stress, cognitive function

Evidence on the microbiota-gut-brain axis demonstrates that the gut microbiota plays a significant role in cognition, which can be compromised when the intestinal microbial community is disrupted. Interventions that promote the growth of beneficial gut bacteria, including prebiotics, have been shown to positively influence cognitive outcomes[22]. A recent review of human prebiotic intervention studies reported that chronic prebiotic supplementation (>28 days) improved affect and verbal episodic memory compared to placebo. Acute prebiotic interventions (<24 hours) also showed benefits, particularly for cognitive variables such as verbal episodic memory[23]. The mechanisms underlying gut-brain signaling have been explored mainly through *in vitro* and animal studies[24]. Several potential pathways have been proposed, including SCFA production that affects the hypothalamic-pituitary-adrenal axis, endocrine mechanisms involving microbial production of neurotransmitters and hormones, immune pathways linked to the release of anti-inflammatory mediators or neural communication through vagus nerve stimulation. Whilst there are human randomized controlled trials demonstrating that certain prebiotics have a positive effect on cognitive health, there are currently no EFSA-approved prebiotic health claims relating to cognitive function in the EU.

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