Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Biotechnology

# Novel probiotics and prebiotics: road to the market☆

Himanshu Kumar[1], Seppo Salminen[1], Hans Verhagen[2,3], Ian Rowland[4], Jim Heimbach[5,6], Silvia Bañares[7], Tony Young[8], Koji Nomoto[9] and Mélanie Lalonde[10]

Novel probiotics and prebiotics designed to manipulate the gut microbiota for improving health outcomes are in demand as the importance of the gut microbiota in human health is revealed. The regulations governing introduction of novel probiotics and prebiotics vary by geographical region. Novel foods and foods with health claims fall under specific regulations in several countries. The paper reviews the main requirements of the regulations in the EU, USA, Canada and Japan. We propose a number of areas that need to be addressed in any safety assessment of novel probiotics and prebiotics. These include publication of the genomic sequence, antibiotic resistance profiling, selection of appropriate *in vivo* model, toxicological studies (including toxin production) and definition of target population.

**Addresses**
[1] Functional Foods Forum, University of Turku, Itäinen Pitkakatu 4a 5ks, Turku 20520, Finland
[2] National Institute for Public Health and the Environment (RIVM), PO Box 1, 3720 BA Bilthoven, The Netherlands
[3] University of Ulster, Cromore Road, Coleraine, BT52 1SA Northern Ireland, United Kingdom
[4] University of Reading, Reading RG6 6AP, United Kingdom
[5] JHeimbach LLC, 923 Water Street, P.O. Box 66, Port Royal, VA 22535, USA
[6] Dairy & Food Culture Technologies, Centennial, CO 80122, USA
[7] Abad Oliba – CEU University, Bellesguard, 30-08022 Barcelona, Spain
[8] Kleinfeld, Kaplan, and Becker LLP, USA
[9] Yakult Central Institute, Kunitachi, Tokyo 186-8650, Japan
[10] Bio-K Plus International Inc., 495 boul. Armand-Frappier, Laval, QC, H7V 4B3 Canada

Corresponding author: Salminen, Seppo (sepsal@utu.fi)

**Current Opinion in Biotechnology** 2015, **32**:99–103

This review comes from a themed issue on **Food biotechnology**

Edited by **Michiel Kleerebezem** and **Christophe Lacroix**

http://dx.doi.org/10.1016/j.copbio.2014.11.021



## Introduction

Issues pertaining to novel probiotics and prebiotics has increased in importance due to the fast-paced research in human microbiome science. Tools to manipulate the gut microbiota for improving health outcomes are in demand as the importance of the gut microbiota on health is revealed. Some probiotics and prebiotics have been used for decades, but probiotics and prebiotics targeted toward unique outcomes and functionalities can be expected to emerge.

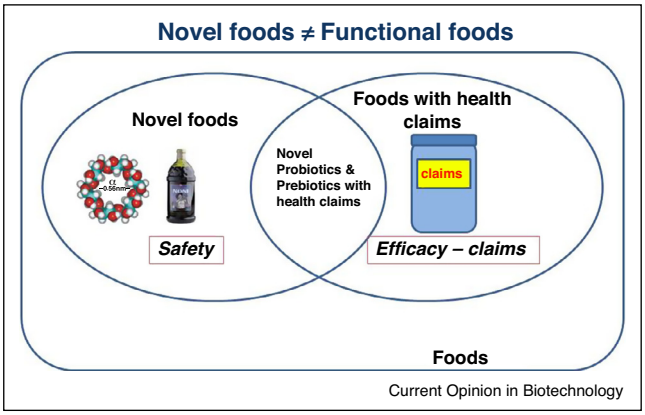
The regulations governing introduction of novel probiotics and prebiotics vary by geographical region. In some cases, confusion can result in differentiating novel foods from functional foods. The fundamental difference between these two categories of foods is that novel foods must be evaluated based on their safety, whereas functional foods need to be evaluated for any desired health claims. Figure 1 demonstrates that the terms are distinct but sometimes foods and food ingredients fall in both categories, which then necessitates evaluation for both safety and efficacy. This review summarises the discussion group views on current legislative framework in the USA, Europe, Canada and Japan regarding the assessment of probiotic and prebiotic novelty from the scientific, regulatory and consumer viewpoint. Additionally, it highlighted some of the major hindrances observed for 'novel' probiotics.

## What are 'novel' probiotics and prebiotics?

In a recently published consensus report, the term 'probiotic' as originally defined by FAO/WHO was endorsed with minor corrections as 'live microorganisms that, when administered in adequate amounts, confer a health benefit on the host' [1••]. The Food and Agriculture Organisation of the United Nations (FAO) defines 'prebiotic' as 'a nonviable food component that confers a health benefit on the host associated with modulation of the microbiota' [2]. Previously, prebiotic studies were focussed on inulin, fructo-oligosaccharides and galacto-oligosaccharides and these prebiotics are now in the USA generally regarded as safe because of their long history of safe use.

☆ The International Scientific Association for Probiotics and Prebiotics (ISAPP) organised a discussion group comprising experts from probiotic research, industry and regulatory authorities from the United States, United Kingdom, Spain, the Netherlands, Finland, Canada and Japan during the 12th annual meeting in Aberdeen (Scotland), to characterise the requirements to be fulfilled and to establish differences in the path to the market for novel probiotic and prebiotic products.

**Figure 1**




Differences between novel foods (foods not previously consumed to a significant degree, and evaluation for safety) and foods with health claims (evaluated for efficacy).

Probiotics and prebiotics may also be novel foods, leading to challenges on whether or not a food or food ingredient is 'novel' especially in the EU [3•]. In the regulatory field, 'novel' is a legal construct determined by law, typically in relation to developments that occur after the regulation was enacted, thus leading to scientifically recognized grey area of novel foods [3•,4]. For the purpose of this paper, 'novel' will be used in the regulatory sense.

New probiotics and prebiotic components with varying functions have emerged. In the EU, these may be recognized as 'novel foods', thereby triggering a risk assessment procedure. In each case, the novel status will be assessed on a case-to-case basis. For example, a fructo-oligosaccharide or galacto-oligosaccharide with a significantly different degree of polymerization or with a different source or production method might be regarded as novel.

## Regional differences in regulation of probiotics and prebiotics with respect to novelty and safety

### European Union

Worldwide, the regulations governing novel foods, functional foods and traditional foods vary. In the EU, the introduction of novel foods that have not been used in the EU prior to 15 May 1997 is governed by the Novel Food Regulation 285/97/EC [5]. This Regulation clearly defines the risk assessment steps required for any authorisation of the novel food prior to introduction into the EU market. The regulation also defines 'substantial equivalence' to commonly used foods and in which case a simplified notification procedure applies. The Novel Food Regulation from 1997 is currently under revision and a proposed new regulation was published in December 2013 [6]. Potential changes in the update of the Regulation may cover traditional foods from 3rd countries, nanotechnology, as well as the submission and evaluation route (i.e. directly to EFSA rather than being conducted by competent authorities in member states) [6].

Based on the Regulation, a member state competent authority or European Food Safety Authority (EFSA) and the European Commission (EC) can make assessments of any food or food ingredient that has no history of safe use prior to 1997 in Europe and hence can be identified as 'novel'. The Regulation then requires an extensive safety assessment of the food or ingredient prior to acceptance to the EU market [4]. A list of novel foods and ingredients is available in the public registry by the EC and approvals are also explained in an inventory specifying the uses and restrictions for each component (http://ec.europa.eu/food/food/biotechnology/novelfood/nfnetweb/mod_search/index.cfm). For bacteria added into foods, which could also be considered novel [3•,4], there is an annually updated list of microbes intentionally added to foods (QPS, Qualified Presumption of Safety of Micro-organisms in Food and Feed, list) and this list forms the basis of organisms at the species level which are considered safe for foods and feeds in European Union (EFSA 2013 update) [7].

A novel probiotic or prebiotic can potentially be a component of conventional foods, food supplements or foods for particular nutritional uses ('Parnuts'). Parnuts foods incorporating probiotics or prebiotics comprise those designed for specific dietary requirements and may include infant formulas and follow-on formulas, processed cereal-based food and baby food, food for special medical purposes and total diet replacement for weight control.

When designated as a novel food, a safety assessment follows the European Novel Foods Regulation [3•], and an evaluation is needed for the EC to make a decision on the safety of the novel component.

The EC regulation on nutrition and health claims 1924/2006 requires that such claims are based on scientific evidence and acceptability [8]. EFSA has provided scientific and technical guidance for presenting applications for health claims on food. Neither Parnuts Directive 2009/39/EC nor EU Regulation 609/2013 are an escape route to circumvent the Health Claims Regulation 1924/2006; Hendriksen and Verhagen have developed a decision tree to discern Parnuts foods from ordinary foods (with health claims) [9•]. Following on from the publication of the health claims Regulation 1924/2006 [8], the EFSA has now evaluated about 3000 health claims for being scientifically substantiated (or not substantiated) [10].

### United States

In the United States, all foods and food ingredients are regulated under the Food Drug and Cosmetic Act (FDCA). Safety of new and novel foods in the United