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Probiotics and prebiotics in infant formula: regulatory status and innovation

Breastfeeding: a natural source of probiotics and prebiotics

Probiotics have no "legal" definition, but can be considered as "living microorganisms, which when administered in adequate amounts confer health benefits on the host" following the description provided by FAO/WHO (2006).

Prebiotics, in turn, are usually deemed as "non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already established in the colon, and thus in effect improve host health" in accordance with the definition provided by Gibson and Roberfroid (1994). Even though they are generally added to food intentionally, probiotics and prebiotics are naturally occurring substances (with a few exceptions). One of the most widely studied natural sources of probiotics and prebiotics is human milk because of its high content in bacteria and numerous oligosaccharides. Significant advances in this area over the past years have helped to greatly narrow the distance between human milk and formula milk. However, seeing the exact properties of human milk reproduced in milk formulas – the holy grail of the industry – will take more research and development and a more pragmatic approach from regulators.

The role of prebiotics and probiotics in human milk

Breastfeeding is still the preferred nutrition option amongst paediatricians and health professionals worldwide because it provides the adequate nutrients for infants. However, the main reason behind it does not only lie on its optimal nutritional composition, but also on other substances and compounds providing active and passive immunity to infants. Human milk is a powerful immunomodulator containing a large number of different enzymes, hormones and other substances which enhance and aid the development of infant immunity systems in early life (Hemarajata and Versalovic, 2013). It is also a rich source of probiotic bacteria: hundreds of species have been isolated so far (Li S.W. *et al.*, 2017), with *Lactobacillus* and *Bifidobacterium* genus being especially relevant to human milk immune properties. The beneficial effects of these bacteria on the immune system are well-known by the scientific community. These naturally present bacteria will colonise the gut during the first stages of life and play an important role in aiding the development and preservation of the integrity of the intestinal mucosal barrier. The scientific consensus is that probiotics mainly exert their function by competing with pathogens for nutrients and binding sites on the intestinal epithelium, hence altering the composition of the microbial community. However, different studies propose additional mechanisms linked to their immunomodulation effect: production of antimicrobial substances, bacterial growth inhibitors, enhancement of the intestinal barrier and modulation of human intestinal cells gene expression (Daliri and Lee, Byong, 2015). In addition, it is important to note that a correct balance of the microbial community (and their microbiome) is tightly linked to future disease susceptibility and prevention (constipation, allergies, etc.).

Although the presence of bacteria in high numbers in the milk is partly responsible for the changes in the intestinal microbial communities, it is not the only factor modulating the intestinal bacteria balance. Nutritional compounds in human milk, mainly (but not exclusively) oligosaccharides, will also play a part in maintaining a good balance as this fraction will be selectively metabolised by beneficial bacteria. The fermentation of those carbohydrates will further promote the settling and growth of the bacteria and will result in the production of immunomodulating substances such as short chain fatty acids (Gibson and Roberfroid, 1994).

Probiotics and prebiotics in infant and follow-on formulas: regulatory status

However, regular milk, which is used in the manufacturing of infant formula (IF) and follow-on formulas (FOF), cannot shape infant immune systems as human milk does. For that purpose, probiotics and prebiotics have been added to IF and FOF for a long time to supply the lack of naturally present immunomodulators. Research and innovation in those products aim to mimic human milk's natural content in nutrients, prebiotics and probiotics to provide non-breastfed infants the same health benefits. Special remarks should be made on the development and introduction of synthetic human milk oligosaccharides in the market, which have played an invaluable role in the refinement of IF and FOF. Surprisingly, despite the wide use of live microorganisms in infant formulas over the past decades, the use of probiotics is still not regulated by specific laws in the EU. Its use in IF and FOF is only supported by Article 5 to Directive 2006/141/EC, which states that other ingredients (in addition to the ones disclosed in the same law) may be added to IF if their safety and suitability for infants can be proven based on scientific evidence. In addition, Regulation (EC) No. 1333/2008 specifies that non-pathogenic L(+)-lactic acid producing cultures are allowed to be used in the manufacturing of acidified milks. Nevertheless, the addition of prebiotics, in the form of fructo-oligosaccharides and galacto-oligosaccharides, is explicitly permitted under the same Directive. It is to be noted that Directive 2006/141/EC supposed a big step for the industry as it enabled health claims to be used in IF and FOF, while the old Directive 91/321/EC only allowed nutritional claims. The list of authorised nutrition and health claims in IF and FOF is disclosed in Annex IV to Directive 2006/141/EC. Nevertheless, no health claim in IF and FOF has been authorised so far, and only protein hydrolysates can bear a claim describing its role in reducing the risk of developing allergy to milk proteins.

If we carefully assess the reasons behind the lack of legal framework for probiotics in infant formula, we would probably find the answer in the unsuccessful reduction of disease risk claim petitions issued under the provisions established in Article 14(b) to Regulation (EC) No. 1924/2006. EFSA has repeatedly expressed an insufficient characterisation of the microorganisms and a weak correlation between their consumption and the claimed effect. So far, the authorities have not approved any claim on probiotics. Moreover, EFSA published its *Scientific opinion on the essential composition of infant and follow-on formulae* in 2014, where the scientific evidence behind the use of probiotics and prebiotics in IF and FOF was assessed.

The opinion described how the available scientific studies showed inconsistencies and limitations that did not allow conclusions to be drawn on the claimed beneficial effects. The Panel concluded that there was no need to include probiotics in IF and FOF but considered that its consumption does not raise any health concern. Based on the same arguments, the Panel drew the same conclusion for non-digestible oligosaccharides. Considering that the effect of prebiotics is strongly linked to that of probiotics, the lack of health claims related to prebiotics is unsurprising. Unfortunately, manufacturers will see their efforts thwarted after 22 February 2020 (21 February 2021 for protein hydrolysates) when the old Directive 2006/141/EC will be repealed and replaced by Regulation (EC) No. 609/2013. After that date, health and nutrition claims will be forbidden on IF and FOF in accordance with Article 8 to Commission Delegated Regulation (EU) No. 2016/127 supplementing Regulation (EC) No. 609/2013 in an attempt to protect breastfeeding. Unfortunately, this prohibition will limit the already restricted marketing strategies for IF and FOF.

In conclusion, there is still a long way to go until probiotics and prebiotics are recognised by the European authorities as indispensable components in IF and FOF. The very unpromising regulatory framework for IF and FOF will take its toll on prebiotics and probiotics by forbidding the use of any health and nutrition claims. The support of independent researchers and the food industry will be key to presenting probiotics and prebiotics as powerful tools for ensuring the development of healthy infants. More clinical studies with robust and improved methodologies will be needed to demonstrate their potentially beneficial effects before the European authorities.

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