Submitted to
**Food Standards Australia New Zealand (FSANZ)**

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# APPLICATION TO AMEND THE AUSTRALIA NEW ZEALAND FOOD STANDARDS CODE: JENNEWEIN 2'-FL IN INFANT AND TODDLER FORMULAS

## EXECUTIVE SUMMARY

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Jennewein Biotechnologie GmbH (Jennewein) is seeking permission to amend Schedule 26 (Food produced using gene technology) of the Australia New Zealand Food Standards (FSANZ) Code (the Food Standards Code) to include Jennewein's 2'-Fucosyllactose (2'-FL) substance as an ingredient in infant formula (from birth to <12 months of age), follow-on formula (from 6 months to <12 months of age), infant formula for special dietary uses, and formulated supplementary foods for young children (FSFYC) i.e. toddler formula (1 – 3 years of age).

In this Application, the Jennewein substance will be referred to as "Jennewein 2'-FL" to distinguish it from naturally occurring 2'-FL. Jennewein intends to provide Jennewein 2'-FL produced from genetically engineered *Escherichia coli* B strain *(E. coli* B strain*)* to manufacturers for use in infant and toddler formulas in Australia and New Zealand. The Jennewein 2'-FL substance will be commercially available in two versions (physical forms) with identical sugar compositions: 1) As a spray-dried lyophilised powder and as a liquid concentrate comprising 45% (w/v) 2'-FL content. The two products will be marketed as "2'-fucosyllactose powder" and "2'-fucosyllactose concentrate", respectively.

2'-FL is a naturally occurring oligosaccharide found in human milk and is one of the most abundant human milk oligosaccharides (HMOs). The intended benefit of adding Jennewein 2'-FL to infant formula, follow-on formula, and toddler formula is as a nutrient necessary for the body's nutritional and metabolic processes. Consistent with naturally occurring HMOs, Jennewein 2'-FL does not undergo any significant digestion in the upper gastrointestinal tract, and serves as a prebiotic for commensal gut bacteria. These bacteria metabolise prebiotics into short-chain fatty acids, which are used by colonocytes in energy production and as a stimulant for sodium and water absorption. Scientific evidence suggests additional infant health benefits from consumption of 2'-FL and other HMOs which include:

- inhibiting the adhesion of pathogenic bacteria and norovirus virus-like particles;
- beneficial impacts on learning and memory;
- reduction in inflammatory intestinal cells;
- enhancing innate immunity to respiratory syncytial virus;
- positively impacting the maturation of cultured intestinal cells and gut motility; and
- a reduction in respiratory and gastrointestinal illness.

A scientific Expert Panel convened by Ramboll determined that Jennewein 2'-FL is "Generally Recognised as Safe" (GRAS) for use in infant formulas and toddler formulas, and Jennewein has received a "no questions at this time" letter from the United States Food and Drug Administration (USFDA) regarding this determination (GRAS Notification (GRN) 571); at a level of 2 g/L of formula, as consumed. Additionally, the Committee on Safety Assessment of Novel Foods in the European Union (EU) determined that 2'-FL can be safely used as an ingredient in infant formulas and follow-on formulas at a level of 1.2 g/L of formula, as consumed. Health Canada issued a Letter of No Objection to the use of 2'-FL produced from *E. coli* BL21 (DE3) strain as an ingredient in formula for term infants at levels up to 1.2 g/L of formula, as consumed. Since 2016, the Jennewein 2'-FL substance has been used in infant and toddler formula products sold in the United States, and in 2017 and 2018 has been launched in products sold in Hong Kong, Singapore, and Mexico and other countries; with Jennewein 2'-FL levels up to 2 g/L per serving.

Jennewein manufactures their 2'-FL using a genetically engineered *E. coli* BL21 (DE3) strain as a processing aid. The fermentation process does not use antibiotics nor any other inhibitors, and the manufacturing process does not use organic solvents or other toxic substances. The production process is ISO 22000 certified and fulfils the requirement for Kosher and Halal food standards. Analyses demonstrate that the Jennewein 2'-FL does not contain any recombinant DNA material or proteins.

Jennewein demonstrated and confirmed the purity of the product and its manufacturing consistency by meeting specifications with five unique production batches, as demonstrated in the certificates of analysis.

The resulting product is 100% carbohydrate and consists of > 90% 2'-FL, with residual amounts of common mono-, di-, and trisaccharides closely related to 2'-FL which are also present in human milk (lactose, difucosyllactose, 3-FL, fucose, glucose and galactose) and a breakdown product, fucosylgalactose, that occurs naturally in the human body. Jennewein 2'-FL is manufactured to meet strict specifications and the resulting product is well characterised through rigorous analytical testing. Jennewein used established analytical techniques to confirm that the identity and structure of Jennewein 2'-FL is the same as human milk 2'-FL. These data demonstrate that the Jennewein 2'-FL is substantially chemically equivalent to human milk 2'-FL.

Toxicological studies with Jennewein 2'-FL demonstrate that it is safe for consumption by rats at dietary fortification levels greater than 7.7 g/kg of body weight (bw)/day and was well tolerated by neonatal pigs at dietary fortification levels of 2.0 g/L/day which corresponds to approximately 299 mg 2'-FL/kg bw/day. Studies also demonstrate that Jennewein 2'-FL is not mutagenic or genotoxic. Additionally, Jennewein 2'-FL does not contain residual components from the manufacturing process with allergenic potential and there is no evidence to suggest that it may cause adverse effects in sensitive populations.

For use in infant formula, follow-on formula, infant formula for special dietary uses, and toddler formula, the proposed use is up to 2 grams (g) Jennewein 2'- FL per litre (L) of formula; which represents the naturally occurring level of 2'-FL in human milk. Based on this intended use, the highest estimated mean intake of Jennewein 2'-FL is 1.6 g per day for infants 0 to <6 months of age (based on a formula intake of 0.8 L/day), 1.2 g per day for infants 6 to <12 months of age (based on a mean formula intake of 0.6 L/day), and between 0.6 and 0.8 g per day for young children (toddlers) 1 to 3 years old (based on a mean formula range of 0.3 to 0.4 L/day). Some infants and toddlers, however, consume a combination of human milk and infant or toddler formula. Because the proposed use level of 2 g/L is equivalent to the mean concentration of 2'- FL normally found in breast milk, the overall intake of 2'-FL by combination breast milk/formula fed infants and toddlers is unlikely to differ significantly than the estimates provided in this Application.

In summary, the available scientific evidence obtained from studies performed using Jennewein 2'-FL, clinical studies performed using infant formula supplemented with synthesised 2'-FL and the history of safe consumption of 2'-FL from human milk, supports the safe use of Jennewein 2'-FL in infant formula, follow-on formula, infant formula for special dietary uses, and toddler formula. It is anticipated that approval of Jennewein 2'-FL as a nutritive substance produced using gene technology in Australia and New Zealand will positively benefit infant and young children's health and industry by allowing for the increased availability of innovative infant and toddler formula products that more closely replicated the composition of human milk.

The Australian New Zealand Food Regulation Ministerial Council's regulation on infant formula products states that "the composition of breast milk should be used as a primary reference for determining the composition of infant formula and follow-on formula". Therefore, the addition of Jennewein's 2'-FL to infant formula and follow-on formula is consistent with these efforts to produce infant formula products with ingredients that closely match the naturally occurring nutrient composition of human milk. The addition of Jennewein 2'-FL to FSFYC (i.e. toddler formula) is aligned with the same goal of creating a product with ingredients, in particular, HMOs, that are equivalent to those in human milk. Toddlers are expected to obtain similar health benefits conferred to infants due to the same effects of the ingredient.