Submission to
Food Standards Australia New Zealand

Consultation paper 1 – Safety and food technology
Proposal P1028—Infant formula

7th July 2021

Introduction

This submission on behalf of Danisco Australia and Danisco New Zealand, is made in response to Consultation paper 1 – Safety and food technology to Proposal P1028—Infant formula.

Danisco/IFF

Danisco operates in Australia and New Zealand as subsidiary of International Flavors and Fragrances Inc (IFF), manufacturer/marketer of specialty food ingredients (including probiotics), food additives, flavourings and food processing aids.

Upon consideration of the topics discussed in Consultation Paper 1 we welcome the opportunity to provide comment, to Food Standards Australia New Zealand on the Regulation of Infant Formula Products in respect of safety and food technology.

General Comment

Danisco supports the primary objective of FSANZ's P1028 review to protect public health and safety. We also agree with the premise that Infant formula must be safe for formula-fed infants to consume, and caregivers need to know how to safely prepare, use and store the product. It is also our general position that the FSANZ Standard 2.9.1 Infant Formula products should, where FSANZ's primary objectives are satisfied, align with the relevant Regulations and Standards in the EU and CODEX, respectively.

Food Additives

FSANZ have proposed to not permit general carryover of additives in IF and IFPSDU, which is currently the case in both EU and Codex. In principle, Danisco support this approach. Additionally, we are not aware of any instance where the carryover principle has been relied upon for infant formula product marketed in Australia or New Zealand.

With respect to harmonisation of additive permissions, given the situation with respect to IFPSDU in this market being wholly sourced by import predominantly from the Europe Union, it is our strong recommendation that the FSANZ proposal to harmonise additive permissions with the relevant EU regulations on foods for special medical purposes. It follows therefore, that the food class system for food additive permissions should also align with European regulation.

Please see our comments to some of the specific questions raised in Consultation Paper 1 in the following paragraphs. We would like to highlight that we have provided comment only as FSANZ questions relate directly to the interests and expertise of Danisco/IFF within the context of Consultation Paper 1.

FSANZ CP1 Questions for Submitters

Question 2

Table 2.17 lists the proposed approach for food additives. It includes some food additives where it is proposed to align with EU regulations but FSANZ has noted that there is a lack of safety information and therefore, it is not possible to draw a conclusion on the safety of these substances at the proposed levels in the target population. In these cases (all relate to IFPSDU which are generally imported into the Australian and New Zealand market), we request further information from health professionals about the need to permit addition of these food additives to

IFPSDU and information from manufacturers about industry use of these food additives in Australian and New Zealand. The food additives that this question pertains to are:

FSANZ have requested further information from health professionals about the need, and from manufacturers about industry use, of a number of food additives in Australian and New Zealand. We address here specifically the use of Locust Bean Gum in products for reduction of gastro-oesophageal reflux.

Gastroesphageal reflex (GER) is the involuntary passage of gastric contents into the oesophagus and is a common and global problem during early infancy affecting about 50% of all babies up to the age of 2 months (Netzer et al 1996). In the EU and other countries, locust bean gum has been added to infant formula to safely and effectively thicken it in order to manage GER. Thin fluid can cause a lack of coordination with sucking, breathing and swallowing in infants. Consumption of thickened formulas in infants who spit-up frequently results in decreased regurgitation (Vandenplus et al 1994). Studies have shown that infant food formula containing LBG (doses ranging from 0.3-0.5%) as a thickening agent, decreased the number of regurgitation episodes without affecting gastric emptying delay in very young infants with recurrent vomiting (Miyazawa et al 2007). Importantly, an integrated safety review which compiled relevant pre-clinical toxicological studies in combination with substantial evidence gathered from the clinical paediatric use, concluded that LBG is safe for its intended therapeutic use in term-born infants to treat uncomplicated regurgitation from birth onwards (Meunier et al 2007). This safety assessment found that the standard therapeutic level of 0.5 g/100 mL in thickened infant formula confers a sufficiently protective margin of safety.

It is our experience that addition rates for LBG in both locally and internationally marketed Infant formula for thickening to alleviate reflux in infants do not exceed 0.5 g/ml. If there is a justification for higher addition rates, we are not aware.

References:
Netzer et al., Schwiz Med Wochenschr, 1996; 79:53-7
Vandenplas et al., Eur j Pediatr, 1994; 153: 419-23
Miyazawa et al, Acta paediatrica 2007,pp 910-914 .
Meunier et al, Regulatory toxicology and pharmacology 70 (2014) 155 – 169

Lactic acid producing microorganisms

FSANZ has indicated that there had not been broad discussion on the permissions for L(+) lactic acid producing microorganisms in infant formula in the 2016 consultation paper. Accordingly, we present here some background on this topic. We note that some of the mentioned literature was discussed in SD2.

Infant gastrointestinal microflora develops quickly after birth and is linked to development of the immune system. The first exposure for an infant takes place via the mother, who becomes a primary source of bacterial species found in the developing gut microbiota of the infant. Infant nutrition (breast feeding or formula feeding) provides further support for an infant's microbiota growth which continues to develop until 3 years of age. During this period, development of infant microbiota helps drive the maturation of the immune system. The disruption of the development of the microbiota and immunity during this critical period has been linked with the development of allergies and eczema.

Within the probiotics industry, there has been a lack of clarity concerning the appropriate use of probiotic strains as an efficacious ingredient in infant formula. While the health benefits for

infants are widely recognised and have been demonstrated extensively in clinical trials for a number of species of Lactobacillus and Bifidobacterium, the aspect of general acceptance has been compromised by the listing of a limited population of lactic-acid bacteria for use in infant formula as part of a series of Codex reports and standards.

Historically, in a toxicological evaluation of a number of food additives (Food and Agriculture Organization/World Health Organization, 1974), the Joint FAO/WHO Expert Committee on Food Additives considers the safety of lactic acid. A simple statement in this report indicates that there is "some evidence that the neonate has difficulties in utilising the D(-)isomer of lactic acid; it was considered, therefore, that neither this nor the racemate should be used in foods for infants less than three months old. Metabolic studies on the utilisation of D(-)-lactic acid in infants are needed."

Subsequently, the specific listing of "only L(+) lactic acid producing cultures may be used" within the Codex Standards for Infant Formula and Formulas for Special Medical Purposes Intended for Infants (CODEX STAN 72-1981) and also in the Codex Standard for Processed Cereal-based Foods for Infants and Young Children (CODEX STAN 074-1981) was introduced. Combined, these Codex standards together limit inclusion of only L(+)-lactic acid producing cultures to infant (birth to 12 months) and young children (12 months to 3 years), excluding the potential of other probiotic strains. This is problematic for many reasons, as supplementation of infant formula with probiotics has clearly demonstrated health benefits at early stages of life. Numerous clinical studies have demonstrated that this age range is key for optimal microbiota and immune development, and consumption of probiotics during infancy and early childhood has been recognised to render strain-specific health benefits. (Watkins C, 2017) (Milani C, 2017) (Lenfestey MW, 2017) (Deshpande G, 2017).

A review (Reuter, 2001) of the dynamic aspect of human microbiota from birth to late adulthood indicates the distinct nature and complexity of the microbial community at different stages of life. Both indigenous and transient species comprise the microbiota of infants, adults, and elderly. Lactobacillus gasseri and L. reuteri are indicated as the predominant indigenous Lactobacillus species in infants and adults, while species such as L. casei and L. rhamnosus are transient. In infants, the Bifidobacterium species that are often identified are B. bifidum, B. infantis, B. breve, B. parvulorum, and B. longum, while typical Bifidobacterium species for adults include B. adolescentis and B. catenulatum with variants of B. bifidum, B. longum, and B. breve, distinguishing these variants from those found in infants. This microbiota evolution continues, as the diversity and numbers of Bifidobacterium spp. in the elderly is reduced (Reuter 2001) (Arboleya 2016).

While the unique microbiota and potential vulnerability of the infant population is the rationale for excluding the listing of D(-)-lactic acid producing cultures in infant formula and cereal-based foods for young children is not understood. Perhaps the indirect association of D(-)-lactic acidosis in pediatric and adult patients has been assumed to include infants as a vulnerable population whose microbiota is not yet established. However, it should be noted that the documented cases of D(-)-lactic acidosis have been limited to patients whose intestinal tract has been significantly surgically altered, most often linked with short bowel syndrome. (Satoh, 1982) (Munakata, 2010) There have been no reported cases of healthy individuals with elevated D(-)-lactic acid levels, and no link of acidosis to the ingestion of D(-)-lactic acid producing bacteria as probiotics. (Connolly, 2005).

A recent review of D-lactic acid acidosis by Fabian et al. explains that most cases are due to malabsorption, caused by removal of large sections of the intestine, most commonly associated with short bowel syndrome. While normal digestion in a healthy intestine prevents an influx of

carbohydrates to the colon, malabsorption can result in high amounts of carbohydrates in the colon, resulting in fermentation by the colonic microbiota. This can promote a favouring of D(-) and L(+)-lactic acid producing bacteria in the colon. The review by Fabian et al. continues to state that while the colonic microbiota may promote lactic acid-producing bacteria, this may not provide causation to D(-)-lactate acidosis. Data shows that of patients with short bowel syndrome, 82% show elevated levels of D-lactate in stool, but few have increased plasma concentrations of D-lactate and are without acidosis symptoms. Moreover, fecal D-lactate levels may be higher in patients without acidosis than in those with D-lactic acidosis, suggesting that, besides overproduction of D-lactic acid by intestinal microbiota, different factors may be involved in the development of D-lactic acidosis. Furthermore, impairment of metabolism and excretion factors associated with liver disease and chronic renal failure, respectively, are also believed to be involved. (Fabian, 2017).

D(-)-Lactic Acid Analysis in Infants/ Relevant Clinical Studies:
There have been several studies that establish the overall safety of infant formula supplemented with probiotics. Due to the conflicting information of association of D(-)-lactic acid producing cultures and D(-)-lactate acidosis, several studies have addressed this issue in infants specifically, and directly evaluated this hypothesis.

The facet of D-lactic acid accumulation and metabolic acidosis was studied (Haschke-Becher E, 2008) in infants that received infant formula supplemented with a probiotic strain Lactobacillus johnsonii La1. Compared to the infant formula-fed control group, the group supplemented with probiotic strain La1 did not demonstrate any changes in urinary D-/L-lactate excretion at baseline or after four weeks of supplementation. While it is interesting to note that in both infant formula-fed groups, the levels of urinary D-lactate were slightly increased compared to the breast-fed infants, there was no change in D(-)-lactic acid in probiotic group compared to control group, or compared to baseline, indicating that L. johnsonii La1 consumption did not present any accumulation of D(-)-lactic acid or cause for concern of metabolic acidosis. This is especially interesting since an earlier study by LaPierre et al. demonstrated that L. johnsonii La1 ferments lactose to produce a racemic mixture of 60% D(-)- and 40% L(+)-lactic acid. (LaPierre L, 1999)

The safety of lactic acid bacteria and the indirect correlation to elevated D(-)-lactic acid levels, a study was designed to directly monitor D(-)-lactate levels in the blood of infants supplemented daily with a probiotic that produces both D(-)- and L(+)-lactic acid. Lactobacillus reuteri ATCC 55730 was administered as oil drops at 10^8 CFU daily from birth to 12 months of age. Blood samples were taken at six and twelve months of age. There were no differences in D(-)-lactic acid levels between the probiotic and the control group; both of which were very low. (Connolly, 2005).

Another study measured the concentration of D(-)-lactic acid in urine of healthy infants, ages 3 to 12 months, that were supplemented with either B. infantis R0033, B. bifidum R0071, or L. helveticus R0052 at a dose of 3.10^9CFU/day for eight weeks. Safety and tolerance was assessed for each group, and quantification of D(-)-lactic acid in urine was determined to be below the level of detection throughout the study. The authors explain that a thorough literature search confirmed that all cases of D(-)-lactic acidosis were limited to infants with short bowel syndrome, and never documented as related to ingestion of D(-)-lactic acid bacteria in healthy infants. (Manzano S, 2017)

A study by Papagaroufalis et al. also measured the concentration of L(+)- and D(-)-lactic acid in the urine of new born infants fed infant formula supplemented with L. reuteri DSM-17938 at 1.2x10^6 CFU/ml. These levels were compared to baseline, and measured at days 7, 14, 28, 112 (+/- 3 days), and also compared to a control group fed infant formula. Blood pH, weight, height,

and head circumference were also measured, and digestive tolerance was monitored. Results indicated that at days 7 and 14, D(-)-lactic acid levels in the treatment group were slightly higher than the control group, but still within normal range. The levels of D(-)-lactic acid decreased to match the control group by day 28 and remained equivalent between the groups for the remainder of the study. No adverse events contributed to the probiotic were observed. At no time was there any indication of D(-)-lactate acidosis, and the values for blood pH, weight, height, and head circumference were within normal ranges, with no distinction between the treatment and control groups. The overall assessment by the authors was that there was no indication of levels of D(-)-lactate acidosis, and comparison to other studies indicate at all times the concentration of D(-)- and L(+)-lactic acid levels were within normal ranges. The conclusion further states that all documented cases of D(-)-lactate acidosis has been associated with short bowel syndrome or small intestinal bypass, and there has not been any case of probiotic-associated acidosis in healthy infants. (Papagaroufalis , 2014)

The Expansion of Safety Studies for Probiotic Strains in Infant Formula:
Interestingly, there have been a number of studies that indicate that probiotic supplementation is not only safe, but extremely instrumental in providing microbiota and immune system development for ideal infant health. (Watkins, 2017) (Milani, 2017) (Lenfestey, 2017) (Deshpande, 2017) Clinical studies that document the safety and health benefits of probiotic supplementation to infants have also established a continued protective effect throughout childhood, even after discontinued use. (Wickens , 2008) (Wickens., 2012) (Wickens, 2013) Outside of the benefits of microbiota and immune system development, probiotics have been demonstrated to improve gastrointestinal health in infants. (Szajewska H, 2011) (Cameron D1, 2017)

The comprehensive benefits of probiotics to infant health has been recognised globally. As part of a joint FAO/WHO Expert Consultation concerning the use of probiotics in food (FAO/WHO, 2001) the immature nature of infant microbiota is addressed. This FAO/WHO report suggests that for probiotics, demonstration of viability and efficacy for each strain is key. The report also indicates that probiotics may create a microbiota in infants that “improves life-long health”.

While the health benefits and even life-saving benefits of probiotics to infant health has been recognised, the safety of these lactic-acid producing strains has been recognised. The U.S. FDA has acknowledged the safety of a number of lactic-acid producing cultures, including both D(-)- and L(+)-lactic acid producers. The GRAS Notice Inventory (U.S. Food and Drug Administration, 2018) indicates the “no objection” of the use of strains of Bifidobacterium species B. longum and B. breve, the Lactobacillus species L. rhamnosus, L. reuteri, and L. fermentum, also Streptococcus salivarius, and Bacillus coagulans for use in infant formula and/or follow-on formula. The safety of each of these strains has been proven based on phenotypic, genotypic, in-silico, in-vitro, and in-vivo data, most including clinical trials with infant subjects. The safety was not predicated on the production of D(-)- or L(+)-lactic acid production, but on a comprehensive review of all attributes of safety.

Establishing Safety of Probiotic Strains:
The aspect of safety for all “non-pathogenic lactic acid- producing cultures” should be clearly demonstrated. As global regulatory requirements for establishing probiotic strain safety vary, there are core aspects of safety that cannot be overlooked. Of major importance, as outlined in a Safety Decision Tree by Pariza et al., are the origin of the strain, unambiguous identification, whole genome sequence mining for evidence of virulence factor production or toxin production, and antibiotic resistance transfer potential (Pariza MW, 2015). Guidance for determining the risk of transfer potential and acceptance thresholds of antibiotic resistance for probiotic species according to established parameters is recommended. ((FEEDAP)., 2012).

A comprehensive review of the use of probiotics (and prebiotics) in infant health has listed several clinical studies and the results for many conditions and corresponding health benefits. This review included the assessment of probiotic safety, which was summarised as safe for use in infants and children based on current literature, but with the recommendation by the authors that emphasis is put on the oversight of ensuring safety, identity, and genetic stability. (Thomas DW & Section on Gastroenterology, 2010).

Question 13

Does the current permission for L(+) lactic acid producing microorganisms need to be clarified? For example, some L(+) lactic acid producing microorganisms are pathogenic. Do these need to be explicitly excluded (or non-pathogenic specifically permitted) or is the base 'safe and suitable' requirement considered sufficient to manage this risk?

We concur with FSANZ's conclusion is SD2 that for healthy full-term infants, infant formula supplemented with non-pathogenic, non-toxigenic L- and DL-lactic acid producing bacteria does not pose a risk to public health and safety. We also assert that the use of the term 'non-pathogenic' is our preferred approach to clarifying this requirement within the text of the Standard.

To this end, our recommendation would be for Standard 2.9.1 to permit non-pathogenic lactic acid producing microorganisms in infant formula.

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