APPLICATION TO PERMIT THE OPTIONAL USE OF BOVINE LACTOFERRIN IN INFANT FORMULA PRODUCTS

Executive Summary

Applicant:
Synlait Milk Ltd.
[redacted]

Date:
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Synlait Milk Ltd. (Synlait) seeks permission under the Australia New Zealand Food Standards Code (FSC) for the optional addition of bovine lactoferrin (bLf), as a nutritive substance, to foods regulated within the FSC Part 2.9 Special purpose foods, specifically Standard 2.9.1 Infant formula products (infant formula [birth to 6 months], follow-on formula [6 to 12 months] and infant formula for special dietary needs [birth to 12 months]).

The purpose of the use of bLf in Infant formula products is based on the weight of evidence for a reduced risk of infection in formula-fed infants receiving bLf-fortified formula compared to standard formula not fortified with bLf. This is backed up by significant evidence supporting the safe use of bLf in infants. Breastfed infants benefit from lactoferrin naturally present at high levels in human milk. Infants who cannot be breastfed and rely on Infant formula products to support development and growth miss out on the benefits of lactoferrin unless bLf is added to Infant formula products. As well as providing a physiological benefit to formula-fed infants, Infant formula products containing added bLf will more closely reflect the lactoferrin composition in human milk. As the addition of bLf to Infant formula products is already approved in many countries, the ability to include bLf in Infant formula products for sale in Australia and New Zealand will facilitate trade with countries where bLf is already permitted due to exemptions for export of Infant formula products containing added bLf no longer being required. This will help level the playing field for ANZ manufacturers, providing a better competitive position.

Lactoferrin (Lf) is an iron-binding protein that is naturally present in the body. It is present in mammal milks, notably at high levels in human milk (around 1230-1420 mg/L in Australian mothers), and at significantly lower levels in bovine milk (~100mg/L), and consequently infant formula not fortified with bLf (~15mg/L). While bovine and human Lf (hLf) are not identical, differences in structure result in only small differences in cellular uptake and functionality, and bLf has been shown to provide benefits similar to those provided by hLf.

The proposed maximum permitted level of bLf in Infant formula products is 40mg/100kJ across all Infant formula products, which is equivalent to around 1100mg/L made-up infant formula and 1200mg/L follow-on-formula (using the midpoints of the energy ranges in Standard 2.9.1).

Proposed maximum permitted levels of bLf in foods defined within Standard 2.9.1 Infant formula products

Standard	**Target population**	**Specific category**	**Maximum permitted levels**
2.9.1 Infant formula products	Infants 0-12 months	Infant formula	40 mg/ 100kJ
		Follow-on formula	40 mg/ 100kJ
		Infant formula for special dietary use	40 mg/ 100kJ

Synlait bLf is available in powdered form, with specification parameters comprising physical appearance, purity, total bLf levels, moisture, among others, as well as limits for potential chemical and microbiological impurities, and contaminants. Synlait bLf is derived from skim milk using ion exchange technology, a process resulting in a bLf ingredient with high purity and proven bioactivity relevant for infant development.

Based on the totality of information, Synlait concludes there is compelling evidence that a substantial proportion of both intact bLf and its peptides resist gastric digestion and persists throughout the gastrointestinal tract. This resistance to digestion is important for bLf to be able to exert some of its benefits, in particular its bacteriostatic effect. Some bLf is also absorbed in the intestinal lumen via lactoferrin receptors, exerting a range of systemic effects. This duplicity of fates affords it to play a range of different metabolic roles and manifest its bioactivity via a range of different mechanisms. This underlies the clinical benefits associated with the inclusion of bLf in milk-based infant formula products. Based on the results from acute, sub-chronic and chronic animal toxicity studies, Synlait concludes that bLf is well tolerated with no significant adverse effects or toxicity at the concentrations tested. The no-observed-adverse-effect level (NOAEL), based on these toxicity studies, is determined to be 2,000 mg

bLf/kg BW/day. The compound bLf is also non-genotoxic, as determined by the Ames mutagenicity test.

Further support for the safe use of bLf comes from studies in term infants, with normal growth seen in infants receiving bLf at levels up to 1000mg/L made-up formula, and no safety or tolerance issue being reported. Compelling evidence for the safety of bLf also comes from numerous studies in preterm and low-birth-weight infants, a particularly vulnerable population group, with no safety or tolerance issues relating to bLf administration being reported. Administered doses were equivalent to levels of 370-1960mg/L formula. There is also a history of safe consumption of bLf in countries that have had bLf permitted for use in Infant formula products for many years.

There is considerable evidence from *in vitro*, animal and human studies supporting a benefit of bLf in formula-fed infants, notably reduced risk of infection in formula-fed infants receiving bLf versus formula-fed infants not receiving bLf. Several mechanisms underlying this benefit of bLf have been identified, including proven antibacterial effect, antiviral effect, and immunomodulatory effect of bLf. bLf can directly bind to bacteria and viruses and inactivate them, and can bind to receptors in the intestine, blocking entry of pathogens, and can also be internalised and thereby exert immunomodulatory functions. The antibacterial effect of bLf is also partly due to bLf's high affinity to iron. By binding iron, iron is made unavailable to pathogens, which require iron as food. However, iron bound to bLf remains available to the infant, being absorbed together with bLf via lactoferrin receptors. This is supported by evidence from human studies showing that addition of bLf to formula supports normal iron absorption and homeostasis.

Evidence from studies in term formula-fed infants support a reduced risk of respiratory and gastrointestinal infections through bLf addition to infant formula, with both incidence and severity being reduced. Further supporting evidence on reduced risk of infection comes from animal studies. Evidence for a beneficial effect of bLf also comes from the highly vulnerable group of pre-term infants and low-birthweight infants. This population group has an especially high risk of infections, meaning that effective dietary interventions are of particular importance. The use of bLf has been found to reduce the risk of late-onset-sepsis in this vulnerable population group.

Dietary exposure was assessed, and exposure to bLf in formula-fed infants is expected to be somewhat lower than exposure of breastfed infants to hLf. Exposure levels are considered safe. Whilst bLf is an iron-binding protein and contains iron up to 15mg/100g bLf, the contribution of bLf at proposed levels to total iron content in infant formula is negligible. Any iron contributed from added bLf will contribute to the total iron content of formula. Synlait does not anticipate that adding bLf to Infant formula product will have any adverse safety or nutritional outcomes. The addition of bLf to formula increases choice for parents of formula-fed babies, and bLf containing formula may replace formula not containing bLf. Synlait does not anticipate any nutritional concerns with this replacement as any Infant formula products sold in Australia and New Zealand must meet the requirements of Standard 2.9.1 Infant formula products. Based on published evidence, Synlait does not anticipate that parents who are breastfeeding will choose to switch to formula as a result of the addition of bLf to formula.

Overall, there is significant benefit in permitting bLf as a nutritive substance to Infant formula products, in particular physiological benefits for formula-fed infants. There is convincing evidence for the safe use of bLf in Infant formula products.