CONSULTATION PAPER TO FSANZ
(PROPOSAL-P1028-REGULATION OF IFPSDU)

Response to Q19- *Could one category of IFPSDU be used for all additional food additives, or should additional or modified subcategories be devised (noting the possible four subcategories in section 2.2).*

Submitted by

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Executive summary

Infant milk formula (IMF) is a manufactured food designed and marketed for infants under 12 months of age as a substitute for human milk. Continuous research work is being carried out to fortify the IMF with bioactive proteins (lactoferrin, α-lactalbumin, β-lactoglobulin, β-casein etc.) with an aim to bring the IMF closer to human milk. IMF is available in different forms- powder, liquid concentrate and liquid ready to feed (RTF). Among them, RTF liquid infant milk formula is the most convenient type especially when safe water is not available and usually prescribed to preterm, low birth-weight and sick babies. Thus RTF liquid formula could be considered as an Infant Formula Products for Special Dietary Use (IFPSDU). RTF liquid formula is presently processed as a sterilized product by ultra-high temperature (UHT) to ensure safety, however, incurs loss of nutrients due to its high processing temperature (140°C and above). Therefore, pasteurized RTF liquid formula fortified with heat-sensitive bioactive protein could be added as a new category of IFPSDU.

Industrial relevance: Bioactive proteins exert unique health benefits. It is necessary to explore the impact of thermal processing of RTF liquid formula containing bioactives and assess their stability during processing and shelf life. Therefore, the key challenge for the industry is to manage the processing methods so as to minimise loss of bioactive proteins.

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1. Background

Infant Milk Formula (IMF) is designed as a substitute for breast milk for infants under 12 months of age who cannot be breastfed or whose mothers decide not to breastfeed. The goal of IMF is to mimic the growth rate of the breastfed infants along with the potential advantages in prevention of infectious diseases (Beaudry et al., 1995), neurodevelopment (Mortensen et al., 2002) and protection from chronic diseases in childhood (Saarinen and Kajosaari, 1995). However, human-milk composition varies considerably within individuals over time, while the content of IMF generally remains constant (Ballard and Morrow, 2013).

There are three types of IMF available in the market- powder, liquid concentrate and ready to feed (RTF) liquid. Among them, both powder and liquid concentrate forms need to be mixed with water before use whereas ready to feed (RTF) form is served as ready for feeding. RTF liquid formula is usually prescribed to preterm, low birth-weight and sick babies and available in the USA and European market. Conversely, it is restricted as a hospital-only product in some countries like Australia, New Zealand, Singapore etc. Thus RTF liquid formula could be considered as Infant Formula Products for Special Dietary Use (IFPSDU).

Currently, RTF liquid formula is manufactured as sterilized product by Ultra High Temperature (UHT) where temperature of above 135ºC for 2 to 5s is applied (Montagne et al., 2009). However, in general, milk processed using high temperature is of a great concern as heated milk is subject to Maillard reactions, a chemical reaction between amino groups and reducing sugars. van Boekel (1998) summarized the consequences of this reaction for milk and milk products and reported that Maillard reaction exhibits- formation of brown colour , initiation of cooked flavour, nutritional loss etc. Heat also induces less solubility of milk proteins and damages vitamins along with disturbance to the mineral balance (Elliott et al., 2003). Moreover, Perkins and Deeth (2001) observed lower organoleptic acceptability of UHT milk than pasteurized milk among Australian consumers due to its stronger cooked flavour. These negative aspects will also be present in sterilized liquid formula which is of concern.

On the other hand, in order to minimise the gap in composition and effects between IMF and human-milk, researchers and manufacturers are focusing on addition of heat-sensitive bioactive ingredients (lactoferrin, α-lactalbumin, β-lactoglobulin, β-casein etc.) as advised by Codex Alimentarius Commission (Codex, 2007). Therefore, RTF liquid formula, fortified with bioactive proteins, could be manufactured as a pasteurized product to maintain nutritional balance. Thus pasteurized RTF liquid formula, a new product fortified with heat-sensitive bioactive proteins, could bring new scopes to research and manufacturing.

2. Objective(s) of this submission

This submission aims to respond to the Q19 (copied below) of the FSANZ call for consultation on IFPSDU.

Q19: *Could one category of IFPSDU be used for all additional food additives, or should additional or modified subcategories be devised (noting the possible four subcategories in section 2.2).*

This submission would like to emphasize the importance of addition or modification of subcategories for IFPSDU where the special type of fortified formula (e.g; Pasteurized RTF liquid formula) would be specified.

3. Rationale

Considering the addition of heat-sensitive bioactive proteins into RTF liquid formula, this submission is focused on the route to come-up with a pasteurized and fortified RTF liquid formula. IFPSDU could be fortified with multifunctional whey proteins. Among several bioactive proteins, this submission would like to enumerate the possibilities of lacotferrin (LF) and alpha lactalbumin (α-lac) -two heat-sensitive proteins that could be added into pasteurized RTF liquid formula. It is expected that pasteurization would retain substantial amount of protein, added to improve RTF liquid formula.

3.1 Lactoferrin (LF) as ingredient of IMF

3.1.1 Role of lactoferrin (LF)

LF is a globular glycoprotein of about 80 kDa which is widely represented in various secretory fluids (Masson et al., 1966), e.g., milk, saliva, tears and other secretions, and in white blood cells (Baggiolini et al., 1970). It has been reported that the structure of LF is similar in human milk (Anderson et al., 1989), bovine milk (Moore et al., 1997), horse milk (Sharma et al., 1999), and buffalo milk (Karthikeyan et al., 1999).

Strong iron-binding affinity of LF allows it to compete with bacteria for iron which causes inhibition of their growth (Lönnerdal and Iyer, 1995). Wakabayashi et al. (2008) reported that iron-sequestering capacity of LF is responsible for this antibacterial activity. LF shows antiviral activity against both DNA- and RNA-viruses, including rotavirus, respiratory syncytial virus, herpes viruses and HIV (Jenssen and Hancock, 2009; Van der Strate et al., 2001). The antiviral effect of LF lies in the early phase of infection where LF prevents entry of virus into the host cell, either by blocking cellular receptors, or by direct binding to the virus particles (González-Chávez et al., 2009; Van der Strate et al., 2001). LF has also been shown to prevent biofilm formation in mammalian cells. This biological function is related to the ability of inhibiting microbes from adhering, colonizing and forming biofilm on host cells which is a crucial step in the development and persistence of infection. Singh et al. (2002) reported that iron sequestration by LF inhibited biofilm formation by *Pseudomonas aeruginosa* in continuously cultured mammalian cells by twitching (stimulating a bacterial motion). This motion prevents bacteria from attaching to the surface of mammalian cells and ultimately forming biofilm. This activity was observed even at very low LF concentrations (2 mg/100ml). It is also possible that LF has a prebiotic effect in the small intestines. Peptides produced from pepsin digestion of human LF have been shown to have a stimulatory effect on the growth of bifidobacteria (Liepke et al., 2002). Thus, it is possible that increased colonization by bifidobacteria may limit the growth of pathogens.

The amount of LF is lower in cow-milk (0.1-0.4 mg/ ml) than in human milk (1-3 mg/ ml) (Wakabayashi et al., 2006; Lönnerdal et al., 1976). The European Food Safety Authority (EFSA) also declared LF as a novel food ingredient (NFI) and thereby proposed the concentration of LF in IMF could be as high as 100 mg/ 100 g (EFSA, 2012).

3.1.2 Addition of LF in IMF

Considering the nutritional efficacy and safety issues, research on IMF is aimed to mimic human milk including the similar physiological effects found in breast-fed infants. In this regard, numerous investigations on LF have been performed and hence recommended to add LF into IMF since EFSA accepted and approved bovine-LF as a novel food ingredient (EFSA, 2012). Currently LF is being used in various food items including powdered infant formula, yoghurt, supplemental tablet, sports drinks and beverages (Wakabayashi et al., 2006). The global LF market was valued at USD 81.6 million in 2016 and is expected to be USD 167.9 million by 2025 growing at an anticipated CAGR (Compound Annual Growth Rate) of 8.4% over the forecasted period (Grand View Research Report, 2017). Furthermore, it is reported that the growing demand for IMF coupled with competitive strategies adopted by key industry participants is favouring market growth and, at present, IMF occupies about 40% usage of LF (Grand View Research Report, 2017).

3.2 Increased ratio of α-Lactalbumin (α-Lac) to β-Lactoglobulin (β-Lg) in infant formula

3.2.1 Role of α-Lactalbumin (α-Lac)

α-Lactalbumin is a bioactive protein present in all mammalian milk which is regarded as a component of lactose synthesis with antimicrobial, prebiotic and Ca-binding capacity (Lönnerdal, 2014). Mammary gland secrets α-Lac and galactosyltransferase proteins which eventually form enzyme complex lactose synthase and this catalyzes lactose synthesis from glucose and galactose (Brodbeck et al., 1967). After lactose synthesis, α-Lac dissociates from enzyme complex and becomes an integral part of protein content in human milk which accounts for 41% of whey protein and 28% of the total protein (Heine et al., 1991). The α-Lac content in human milk is 3–4 g/L whereas it is 1 g/L in mature cow milk. Currently, α-Lac enriched IMF is available in the market in both powdered and sterile ready-to-feed (RTF) forms.

3.2.2 Role of β-Lactoglobulin (β-Lg)

β-Lactoglobulin (β-Lg) is one of the main whey proteins in cow milk (3.0–3.5 g/L), accounting for about 50% of the whey proteins. However, interestingly, this protein is not present in human milk (Jackon et al., 2004). Despite having numerous functional and nutritional roles on human health, it is considered as a major reason of cow milk allergy (Wal, 2004). It also showed extreme resistance to digestion as it has even been found at low levels in faecal material (Monaci et al., 2006). Therefore, it would be imperative to reduce this protein content from infant formula because complete removal of β-Lg would deteriorate the function of milk proteins since it is necessary for whey proteins to be associated with casein micelles via *κ*-casein binding (Corredig and Dalgleish, 1999).

3.2.3 Protein content and amino acid balance in infant formula vs. human milk

The standard protein content of infant formula is still a matter of controversy since formula production aims to mimic human milk (Sandström et al., 2008). Human milk contians 9-11 g/L protein (Dewey et al., 1996) while conventional infant formula contains 15g/L (Davis et al., 2008). Escalating demand of low protein infant formula, specially in Asia, resulted mainly from paediatric obesity (Marsh et al., 2016). Moreover, excess protein also places unnecessary strain on immature metabolic organs (Karlsland et al., 1998; Schmidt et al., 2004). Thus the alternative could be reducing the protein content and adding free amino acid into infant formula which would be unphysiological since metabolic consequences of free amino acids are mostly unknown (Sandström et al., 2008). Thereupon, a logical approach would be to modify the protein composition of formula to make it a more suitable for human consumption by increasing the ratio of α-Lac to β-Lg which will yield a formula that will be lower in total protein but will retain the necessary balance of essential amino acids (Davis et al., 2008; Kuhlman et al., 2005; Lien, 2003; Sandström et al., 2008).

3.2.4 Mechanism of increased ratio of α-Lac to β-Lg

β-Lg is particularly rich in the essential amino acids- valine and threonine (Järvenpää et al., 1982) whereas α-Lac has high proportion of amino acids- tryptophan, cysteine and lysine (Lönnerdal, 1994). Amino acid tryptophan is the limiting amino acid in infant formula (Heine et al., 1996) and the precursor of neurotransmitter serotonin (Lien, 2003). The mechanism of increased ratio of α-Lac to β-Lg is to reduce β-Lg in infant formula in order to achieve modified but better plasma amino acid pattern in infants (similar to breastfed infants). This could be attained by adding α-Lac ((also with the help of processing) which has well-balanced composition with high proportion of certain essential amino acids (Chatterton and Holst, 1999; Heine et al., 1991; Holt et al., 1999; Kuhlman et al., 2005; Lönnerdal, 2003; Lönnerdal and Lien, 2003). Thus the formula would have less amount of total protein while meeting the amino acid needs of infants (Davis et al., 2008).

4. Conclusions

In response to Q19, this submission would like to propose addition of a special category of IFPSDU where the type of formula (pasteurized RTF liquid formula fortified with bioactive protein) would be mentioned.

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