Ingredients in infant milks

Oligosaccharides

Oligosaccharides are polymers of simple sugars, usually containing 3-10 simple sugars or monosaccharides. Human breastmilk contains over 200 different oligosaccharides, which account for approximately 1% of its composition, and different mothers produce different sets of human milk oligosaccharides (Petherick, 2010). The complex mixture of oligosaccharides present in human milk is thought to have a bifidogenic effect on the colonic microflora of infants to protect them from the specific hazards in their environment. Oligosaccharides that are considered to have a bifidogenic effect are known as Prebiotics. A bifidogenic effect is an effect that beneficially affects the host by selectively stimulating the growth and/or activity of one or several bacteria in the colon and by so doing improves host health (Gibson and Roberfroid, 1995).

Colonic bacteria produce a wide range of compounds which may have both positive and negative effects on the host. The bacterial genera *Bifidobacterium* and *Lactobacillus* are generally accepted as being among the beneficial species of gut bacteria. *Staphylococci* and *Clostridium* are considered pathogenic and *Enterococci, Bacteroides* and *Streptococci* are amongst the genera considered to have both beneficial and harmful effects (Gibson and Roberfroid, 1995). There is evidence to suggest that postnatal immune development may be altered by influencing the constitution of gastrointestinal bacterial flora (Moro et al, 2006). Infant formula made from cows' milk is virtually free of prebiotic oligosaccharides (Costalos et al, 2008). It has been shown that the colonic microflora of infants fed on human milk is dominated by *Bifidobacterium*, while that of formula-fed infants is more diverse with *Bifidobacterium*, *Bacteroides, Clostridium* and *Streptococci* all prevalent (Yoshiota et al, 1991).

Galacto-oligosaccharides and fructo-oligosaccharides (GOS & FOS)
Simple mixtures of long-chain fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) can be produced commercially from lactose and sucrose and are added to in infant formula in an attempt to reproduce the bifidogenic activity of breastmilk (Moro and Arslanoglu, 2005). Whilst FOS and GOS cannot mimic the complex oligosaccharide content of breastmilk, they have a similar molecular weight and high galactose content to oligosaccharides found in breastmilk.

The EFSA *Scientific opinion on the essential composition of infant and follow-on formulae* (EFSA, 2014) notes that most of the studies which investigated the effect of non-digestible oligosaccharide addition to formula had considerable limitations, including a high drop-out rate, lack of consideration of missing values, unclear sequence generation, unclear achievement of allocation, concealment and/or blinding. EFSA (2014) has concluded, as have previous EFSA panels considering health claims, that there is no evidence for health benefits from the addition of prebiotic oligosaccharides to infant or follow-on formula. Despite this, many claims are still made on both family and health professional websites and in health professional literature about the benefits of adding prebiotics to infant milks.

Current regulations permit the addition of GOS and FOS to infant formula and follow-on formula stating maximum amounts, however they are non-essential ingredients.

Human Milk Oligosaccharides (HMOs)

Oligosaccharides in human milk are complex carbohydrates that are known to support the developing infant's immune system (Doherty et al, 2018). They comprise the third largest component of human milk, after lactose and fat, estimated to be about 20-25g/litre in colostrum and 10-15g/litre in mature milk (Bode, 2012). Three major categories of HMO have been isolated: fucosylated and non-fucosylated neutural HMOs which account for the majority of the HMOs present in human milk, and sialylated acidic HMOs which constitute about 12-14% (Smilowitz et al, 2014). The amount and composition of HMOs in human milk vary between women, over the course of lactation and geographically, and more than 200 free oligosaccharide structures have so far been identified (Ruhaak and Lebrilla, 2012). The amount and variety of these complex carbohydrates are unique to human milk.

There are two HMOs being recreated artificially to add to infant milks. These are analogues of 2'-fucosyllactose (2'-FL) and Lacto-N-neotetraose (LNnT). These two analogues have been commercially available for several years, and whilst they are referred to as HMOs, they are not sourced from human milk but are produced by microbial fermentation using genetically engineered micro-organisms including strains of E. coli and yeast (Sprenger et al, 2017).

The European Food Safety Authority (EFSA) consider these artificial HMOs as safe, novel foods (EU 2017/2470) and have said they can be added to infant formula and follow-on formula in combination in concentrations up to 1.2g/litre of 2'-FL and 0.6g/litre LNnT, at a ratio of 2:1 (EFSA, 2015). This approval relates only to their safety and does not imply any benefits.

Nestlé Nutrition launched three new products onto the UK market in Spring 2019: SMA Advanced Infant Formula, SMA Advanced Follow-on Formula and SMA Advanced Growing up Milk. Nestlé have provided evidence to suggest significant health benefits for the addition of (2'FL) and (LNnT) to infant formula. On the SMA Nutrition health care professional website data is provided from a clinical trial to suggest that infants fed formula which contained these two HMO had 70% lower risk of parent-reported bronchitis, 55% lower risk of parent-reported lower respiratory tract infections and more than 50% lower use of antipyretics and antibiotcs.

These results come from a single trial conducted by Puccio et al (2017), which enrolled fully formula fed infants at 14 days or younger, randomised to either a test or control infant formula for 6 months. The study was sponsored by Nestlé and five of the study authors were employed in Nestlé funded centres. Nestlé also funded editorial assistance for paper preparation.The test and control formula used in the trial were identical apart from the addition of the two artificial oligosaccharides (1.0g of 2'FL and 0.5g LNnT per litre, replacing lactose).The authors provided limited information about the formula saying that it has 67kcal/100ml, contained long-chain polyunsaturated fatty acids, 1.8g protein/100kcal (equivalent to 1.2g/100ml) and a whey casein ratio of 70:30. It should be noted that the Nestlé Advanced range of milks for which claims based on this paper are being made are 100% whey based and therefore not the same as this test formula. The authors acknowledged they did not measure the osmolality of the two products. Families were given the test and control formula for 6 months and then both groups were given the same

unsupplemented follow on formula from 6 months, with complementary foods allowed from 4 months.

The study was conducted between 2012-2015 in Italy and Belgium. The primary outcome measure was weight gain between enrolment and 4 months of age, and the sample size was powered for this outcome. A series of secondary outcomes were included drawing on diary data collected by the parents on stooling, and from structured questions and grids on which parents recorded a range of other variables from colic, flatulence, being irritable and waking in the night to illnesses and medication use. 175 infants were enrolled in the study, but 44 infants (20 in control, 24 in the test group, i.e. 25% overall) withdrew before the 4 month primary outcome measurement. The primary outcome was similar weight gain in both groups, which was to be expected when the test and control formula were identical in nutrient composition. Intake of formula was similar in both groups.

As well as reporting on the primary outcome (weight gain between enrolment and 4 months) the authors reported on a range of secondary outcomes which form the basis of the positive health benefits suggested. However, the study was not powered to look at these outcomes, the study sample was relatively small, some outcomes were only reported for sub-groups or at specific time points, the outcomes were primarily reported by parents and there was no breastfed reference group. GI symptoms (flatulence, spitting up and vomiting) showed no significant difference between the two groups. Stool softness showed no significant difference between the two groups at any visit, except a small (but apparently significant) difference reported at two months. The authors reported that a sub-group of infants delivered by caesarean section (about a 1/3 of the sample) were reported to have colic (based on simplistic categorical parental report) less frequently at four months and simple categorical reporting of child waking was suggested by the authors to show a small but significant difference between test and control formula groups in the first two months only. As described above, this fishing for outcomes at different ages and in sub-groups has highly questionable validity.

When assessing morbidity, there were no statistically significant differences between the two groups in reports of ‘adverse events’ across all the categories investigated, with the authors reporting that the group of ‘infections and infestations’ were ‘*approaching statistical significance’* difference between the two groups. Within the ‘infections and infestations’ category the authors claimed statistically significant differences in the parentally reported outcomes of bronchitis, lower respiratory tract infection, antibiotic and antipyretic use, but some of these differences were at certain time points only. No significantly different outcomes were reported for other infections. These trial findings do not prove health benefits from the addition of the two artificial HMOs to the test formula, and the authors (Puccio et al, 2017) accept that all these findings need to be properly considered in further studies.

A paper published in 2018 by Vandenplas et al (2018) - with an authorship with considerable conflict of interest, including Nestlé Nutrition Institute staff - acknowledged that there are no established benefits for the addition of HMOs to infant formula. This paper reviewed evidence for the addition of HMOs from the past 28 years and concluded that:

‘HMOs are one of the major differences between cow’s milk and human milk, and available evidence indicates that these components do have a health promoting benefit [in human

milk]. The addition of one or two of these components to infant formula is safe and brings infant formula closer to human milk. More prospective, randomized trials in infants are needed to evaluate the clinical benefit of supplementing infant formula with HMOs'.

The artificial HMO 2'FL has been added to Similac formula in the USA for some time where it is marketed as supporting infant immune systems. Abbott make the following claims for their product:

'supports the immune system in the gut.'

'Similac with 2'-FL HMO helps support baby's developing immune system by closing five gaps in immune function between formula-fed and breastfed infants.'

These claims are supported by reference to their own clinical trials. Whilst the data used reported some similarities in rates of absorption of 2'FL at day 42 of the trial between breastfed infants and those fed a supplemented test formula, these similarities were no longer apparent at day 119. Furthermore, while differences were found in the absorption and excretion of 2'FL between the groups, no clinical advantage was shown (Marriage et al 2015).

There is currently insufficient information to suggest a health benefit from the addition of artificially created HMOs to infant milks.

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