

**Artificial human milk oligosaccharides in infant milks: A review of evidence provided by Nestlé for their range of 'SMA Advanced' infant milk products.**

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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 suggested there is evidence for significant health benefits for the addition of the artificially created 'Human Milk Oligosaccharide' (HMO) analogues 2'-fucosyllactose (2'FL) and Lacto-N-neotetraose (LNnT). This statement provides some background information on HMOs and reviews the evidence provided by Nestlé to support the statements made in its marketing material on the benefits associated with the addition of artificial HMO to infant formula.

**What are Human Milk Oligosaccharides and why are they important?**

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 neutral 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 HMO 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.

**What are the 'Human Milk Oligosaccharides' added to the Nestlé formula?**

The two HMOs that are being recreated artificially to add to these infant milks 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 human milk oligosaccharides, 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 food ingredients (Commission Implemented Regulation EU 2017/2470) and have said they can be added to infant formula, follow-on formula and young child 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.

**What do Nestlé say about their new ‘SMA Advanced’ infant milks?**

Marketing material for these products is available:

[https://www.smahcp.co.uk/media/2022/ztc4205-sma-advanced-leave-piece\\_final.pdf](https://www.smahcp.co.uk/media/2022/ztc4205-sma-advanced-leave-piece_final.pdf)

The promotional advert for the products states:

*The SMA® ADVANCED range, containing the latest breakthrough in infant nutrition – human milk oligosaccharides – represents our most advanced formulas yet.*

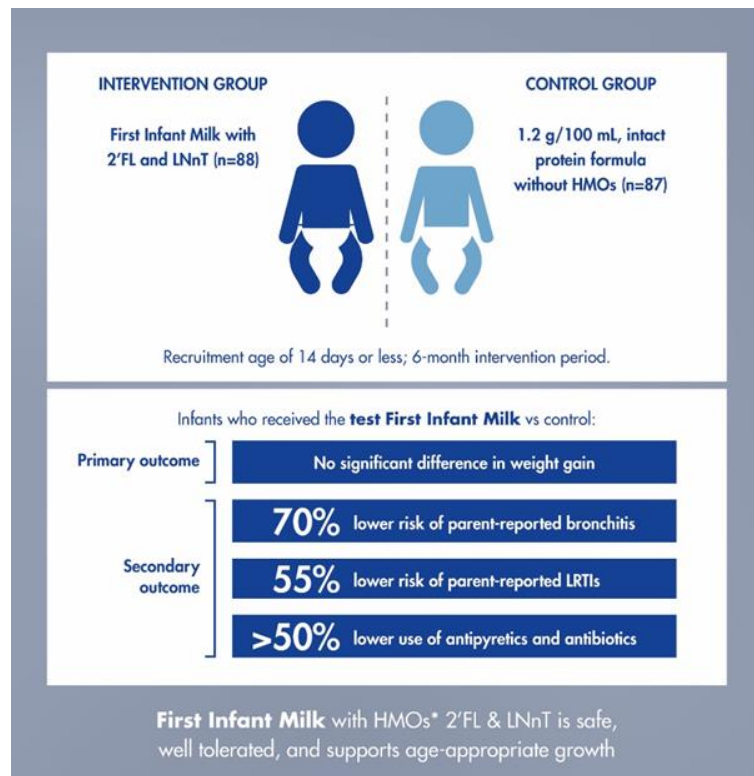
And in very small letters at the bottom of the product advert it says:

*\*HMOs: structurally identical Human Milk Oligosaccharides, not sourced from breast milk.*

We believe that this caveat should be made much more explicit as the impression is given that an ingredient derived from human milk has been added.

In both the marketing material on the website (see infographic below) and in the material being distributed by Nestlé reps to NHS staff (a clinical evidence summary related to the brand rather than a product<sup>1</sup>), they make a series of statements related to the addition of artificial HMOs to infant milks and beneficial health outcomes, all of which are based on data from one study published in 2017 (Puccio et al, 2017).

Website infographic:



<sup>1</sup> A pdf of the SMA Nutrition clinical evidence summary is available on request.



In the SMA Nutrition clinical evidence summary <sup>2</sup> the following statements are made about the benefits of artificial HMO added to infant formula:

Infants who received the test formula (with HMOs) compared to control formula had:

- 70% lower risk of parent-reported bronchitis through 12 months of age
- 55% lower risk of parent-reported lower respiratory tract infections through 12 months of age
- 56% lower use of antipyretics through 4 months of age
- 53% lower use of antibiotics through 12 months of age
- Significantly softer stools at 2 months
- Fewer night-time awakenings at 2 months; in a sub-group of infants delivered by caesarean section, colic at 4 months was reported less frequently

These are significant benefits to suggest from the addition of two artificially processed oligosaccharides to infant milk products. Nestlé associate these benefits with all the products in the 'SMA Advanced' range through the juxtaposition of product information outlining the presence of HMO in the milks with this evidence. It should be noted that the test formula used in the trial was an artificial-HMO supplemented infant formula and therefore suggested benefits cannot be extrapolated to other products.

### **What evidence are these claims based on?**

The claims are based on 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 associated 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. There was no breastfed reference group recruited for this study. 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

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<sup>2</sup> A pdf of this clinical evidence summary available on request.

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, with some information collected from patient records. 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, it is important to remember that:

- The study was not powered to have these as primary outcomes; i.e. it was not designed to be able to detect a difference in these outcomes.
- The study sample was relatively small, which limited its statistical power, created a greater chance of discovering differences which didn't really exist and meant that any differences detected were likely larger than the reality.
- Some outcomes were only reported for small sub-groups or at specific time points. This is sometimes called 'data dredging' where authors look for patterns in data that can be presented as statistically significant, but when the study was not designed or powered to consider these outcomes.
- Many of the outcomes were reported by parents, so are not as objective as those assessed by a clinician.
- There was no reference group of breastfed babies to compare optimal outcomes with these outcomes in fully formula fed babies.

*Secondary outcomes reported:*

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 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, and in recorded antibiotic and antipyretic use, but some of these differences were at certain time points only. No significantly different outcomes were reported for other infections.

**The 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’.*

This review included the Puccio et al (2017) study that is now being used by Nestlé to suggest health benefits related to its new products. Saying that an infant formula might be ‘closer to human milk’ through the addition of artificially created analogue components has no meaning without associated clinical benefits (something can be ‘closer’ but still significantly different).

### **Have HMOs been added to formula elsewhere – and what claims have been made?**

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).

## Conclusion

The importance of HMOs in human milk to infant health is unequivocal, however there remains little evidence to support functional benefit to infants from the addition of artificially created HMO to cows' milk based infant milks. We believe the evidence presented by Nestlé to support the health benefits they have associated with SMA Advanced infant milks is inadequate and misleading. Nestlé have claimed in correspondence to us that they are making no claims for their SMA Advanced products and we encourage health professionals to assess the data provided in marketing materials and reach their own conclusions.

## References

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