

Danone Nutricia Aptamil infant milk reformulation: summary of current knowledge and some questions for the manufacturer.

August 2018

Background

In June 2018 newly formulated powdered Aptamil infant milk products became available in the UK, and there were reports of infants becoming ill after consuming the new product. We produced a statement in July 2018 outlining what we knew about the product changes at that time. This new statement looks in more detail at the evidence provided by Danone Nutricia about the products and poses some questions about the reformulation and the safety and efficacy testing. We will ask these questions to Danone Nutricia but others might wish to also consider these questions when having discussions about the product. We will publish any response we receive.

Changes to Aptamil formulations: what we know.

In June 2018 Danone Nutricia powdered infant formula appeared on the shelves with a new packaging design, and a new 800g weight per carton. Danone Nutricia said they had changed the formulation of their Aptamil brand infant, follow-on and growing-up powdered formula milks, but that this was a change to the process used to make the milk rather than to the formulation itself. A number of small changes to the composition are apparent from the information provided on product datacards. The main ingredient is now lactose, not demineralised whey, there are some minor changes in the amount of lactose, some vitamins and minerals, salt/sodium, inositol and taurine, however none of these are significant. The most significant change is in the whey:casein ratio which is now 50:50, not 60:40, reflecting the decreased amount of whey being used in manufacture. This could potentially have an impact on an infant's stooling and digestion.

We asked Danone Nutricia about the nature of the changes to the formulations and they provided us with a list of references to the trial data used to support the safety of the new product. Danone Nutricia marketing of Aptamil follow-on formula in health professional journals claims that this product now contains a combination of 'prebiotics and postbiotics' which provide benefits to infant health relating to immunity and digestive comfort.

Changes to Aptamil formulations: what the evidence provided by Danone Nutricia suggests has been changed in the product processing.

Danone have patented a process known as Lactofidus™. This involves fermentation of milk with the probiotic bacteria *Bifidobacterium breve* & *Streptococcus thermophiles* followed by a thermal treatment to inactivate the bacteria. The process leaves no viable bacteria in the final product, but their metabolites are present. The rationale for Danone adding fermented milk to their formulas appears to be that in some studies fermented formulas have been associated with alleviation of gut discomfort, and a belief that the addition of prebiotic oligosaccharides (GOS/FOS) has been demonstrated to modulate microbiota development. The hypothesis is that the combination of prebiotic oligosaccharides and the Lactofidus™ process could have complementary and beneficial effects on gut health (Vandenplas et al, 2017).

What is the current evidence for benefit associated with adding prebiotics to infant formula, or for fermented formula?

The clinical benefits of adding prebiotics to infant milks has been widely studied and a number of research studies are used by companies promoting formula with added prebiotics to show health benefits. The European Food Safety Authority (EFSA) *Scientific opinion on the essential composition of infant and follow-on formulae* (EFSA, 2014) concluded, as have the EFSA panel 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.

Fermented milks have been available in other European countries such as France and in African countries where they are marketed as being useful in preventing a range of gastrointestinal symptoms and, in particular, in preventing diarrhoeal disease. Despite widespread use, there is little published data available to support their use. During the fermentation process added bacteria may produce a range of metabolites including lactic acid, lactase and oligosaccharides as well as many others which are as yet unknown (van de Heijning et al, 2014). It is these fermentation products that have been suggested as being responsible for some of the effects on gastrointestinal symptoms reported in clinical trials of fermented infant milks. In 2007 The ESPGHAN Committee on Nutrition carried out a systematic review of the literature to assess knowledge on the effects of fermented infant formula without live bacteria. They concluded that "the published data on the effects of fermented infant formulae without live bacteria are limited and do not allow firm conclusions" (Agostoni et al, 2007). A more recent systematic review (Szajewska et al, 2016) also concluded that from the limited available evidence the use of fermented infant formula without live bacteria, compared with the use of standard infant formula, does not offer clear additional benefit.

What evidence did Danone Nutricia provide to support safety and efficacy of the newly formulated Aptamil products?

Danone Nutricia provided us with the following references to support their claims that the new formulation had been subject to extensive clinical trials. They reported that the studies reported no adverse effects, no negative results related to health and that adequate growth, tolerance and acceptance parameters were reported.

The two studies on which these claims are made are the FIPS Study and the LIFE study. The information on these studies we were given by Danone Nutricia is shown below, but we have given the full references in the reference list at the end of this report.

References to support the FIPS study (clinical trial NTR2521) provided were:

Huet F *et al. J Pediatr Gastroenterol Nutr* 2016; 63(4):e43.
Vandenplas et al. *Acta Paediatr* 2017 106:1150–1158
Vandenplas Y *et al. Arch Dis Child* 2014 99: A91-A92

(NB. Vandenplas et al (2014) is an early abstract about the study later reported by Huet et al, 2016 and provides no additional information about this study so we have not referenced this further)

References provided to support the LIFE study (clinical trial number NTR3455) were:

Herrera AR *et al. J Pediatr Gastroenterol Nutr* 2015; 61:516–517

Rodriguez-Herrera A *et al. J Pediatr Gastroenterol Nutr.* 2016a;62: Abstract N-O-010 (p 658-9)

Rodriguez-Herrera A *et al. J Pediatr Gastroenterol Nutr.* 2016b;62: Abstract G-P-230 (p.422)

Rodriguez-Herrera *et al. Congress EAPs 2016:Poster 0281*

All of the references given for the LIFE study are for abstracts or poster presentations. We cannot locate a peer reviewed paper which fully describes this study.

The FIPS study was funded by Danone Nutricia and staff from Nutricia Research are credited as authors on the paper by Huet *et al*, 2016. We do not have a peer reviewed paper which includes a conflict of interest statement for the LIFE study but staff from Nutricia Research are credited as authors on abstracts.

Questions for Danone Nutricia

Q1. Has the LIFE study been written up in a peer reviewed journal?

Q2. Is the new process used in Aptamil milks marketed in the UK the trademarked 'Lactofidus™' using *Bifidobacterium breve* & *Streptococcus thermophiles* followed by mild heat treatment as mentioned in these clinical trials?

Q3: If not, is a similar fermentation process using the same, or different bacteria, used?

Q4: At what temperature, and for how long, is the fermented milk thermally treated and what procedures are used to test that the product no longer contains viable bacteria?

Q5. Do you know which metabolites from the fermentation process remain in the powdered infant milk products?

Q6. If a fermentation process is used, why do Danone Nutricia not make it clear on the packaging that the milk has been fermented and contains bioactive fermentation products?

Danone Nutricia has said in correspondence that the new formulations marketed in the UK were tested in clinical trials on 1500 babies.

The FIPS study included 432 infants across 3 study centres in France, Belgium and Ireland with 4 study formulas tested. The four study formulas tested were a non-fermented formula with prebiotic (9:1 GOS/FOS), a formula containing 15% fermented formula and prebiotics (9:1 GOS/FOS), a formula containing 50% fermented formula and prebiotics (9:1 GOS/FOS) and a formula containing 50% fermented formula but without prebiotics (Huet *et al*, 2016).

The LIFE study appears to have included 200 formula fed babies randomised to either a formula containing prebiotics combined with 30% fermented infant milk (n=95), or a non-fermented formula without prebiotics (n=105). The abstracts from data analysis of this trial report on growth and safety outcomes and comparative stool consistency of the 2 test formula compared to outcomes for a breastfed reference group of infants (n=100).

These trials did not include test formula of the same composition and not all infants completed these trials. Only a proportion of those in the studies would have received a formula which could be

equivalent to the newly formulated Aptamil products, so it is impossible to say how many babies in these trials the new Aptamil formula marketed in the UK might have been tested on. In the FIPS trial, of the 432 infants included originally only 276 infants (64%) completed the study, We do not have full trial information for the LIFE study to know how many babies failed to complete the study.

Questions for Danone Nutricia

Q7. Which other trials are you including when you say that the new formulation was tested on 1500 babies? Can you provide references for these studies?

Were the test formula used in these studies the same as the new Aptamil formulation available in the UK?

In the FIPS trial the four study formula were isocaloric and contained 66 kcal/100ml, 1.35g protein/100ml, 8.2-8.4g of carbohydrate/100ml and 3.0-3.1g fat/100ml. The Aptamil infant formula now on the UK market has 1.3g protein/100ml, 7.3g carbohydrate/100ml and 3.4g fat/100ml. None of the test formula in this study therefore appear to have the same macronutrient composition as the Aptamil infant formula currently being marketed in the UK.

We have limited information about the LIFE study, however the abstracts and posters that we have been sent by Danone Nutricia suggest that the composition of the intervention formulas in the LIFE study differed from those used in the FIPS study. The formulas used in both studies contained 66kcal/100ml, however the protein content of the test formulas used in the LIFE study were lower than those in the FIPS study (1.2g/100ml v. 1.35g/100ml) and the fat content of the test formulas used in the LIFE study were higher than those in the FIPS study (3.4g/100ml v. 3.0-3.1g/100ml) (Rodriguez-Herrera et al, 2016a). Both sets of test formulas were also different to the Aptamil formula currently marketed in the UK. The full macronutrient composition of the test infant formula used in the LIFE study is not known.

Nothing is known about other components of the test formulas and how these might compare with Aptamil currently marketed in the UK.

Questions for Danone Nutricia

Q8. It does not appear that the test formulas in the FIPS and LIFE trials have the same macronutrient composition as the new Aptamil powdered products being marketed in the UK. Were any of the test formulas used in these studies exactly the same in terms of ingredients and nutritional composition as the product currently being marketed in the UK?

Q9. Is the Aptamil formula currently marketed in the UK based on 15%, 30% or 50% fermented milk with prebiotics (9:1 GOS/FOS)?

Q10. How many infants, overall, have been included in clinical trials testing a product equivalent to the new powdered Aptamil formulations marketed in the UK?

What did the FIPS and LIFE studies show?

In the FIPS study the primary outcome was weight gain. Faecal parameters (short chain fatty acids (SCFAs), acidity, clostridium difficile, secretory IgA, calprotectin) as indicators of an intestinal flora dominated by commensal (beneficial) bacteria were also quantified.

Of the 432 infants originally enrolled, a total of 276 completed the study and 155 dropped out prematurely. This equates to a dropout rate of 36%. The main reasons for dropout included 72 due to an adverse event, 54 due to withdrawal of informed consent, 15 to follow-up and 1 to protocol violation. Among those infants who received any study formula, 28 serious adverse events were reported for 27 (6.5%) infants, 3 of which were reported to be possibly related to the study products. Of the adverse events observed, 154 (37%) included abdominal pain, gastroesophageal reflux or vomiting during the study period. The authors say the number of adverse events reported are typical for young infants and that drop-out rates and reasons for drop-out were similar between intervention groups and therefore they believe there are no safety concerns for use of these products.

The trial reported equivalence in weight gain across all groups and that all formulas were well tolerated, a median parental score of 9 was recorded on an evaluation scale of 0-10. This data is not presented, and it is not clear if this analysis was conducted on the intention to treat or per protocol populations. If it is the latter, then this means those infants who dropped-out due to adverse events or due to withdrawal of informed consent (and that might also be because parents were unhappy with the study products) were not included in the analysis.

Comparing outcomes for the formula with the prebiotics only group, to the prebiotics and 15% and 50% fermented milk groups, showed no difference in faecal parameters. Comparing 50% fermented formula without prebiotics to fermented formula with 50% fermented milk and prebiotics showed significant differences for all parameters except for some of the short chain fatty acids (SCFAs).

The reported data suggested that the presence of fermented milk did not affect faecal characteristics of infants fed a formula with prebiotics and that infants fed with milk that is fermented, but does not contain prebiotics, have different faecal characteristics to infants fed a fermented formula with prebiotics. It seems therefore that it is the prebiotics that affected the reported change in stool characteristics in this study. As highlighted previously the European Food Safety Authority who have reviewed the evidence from studies reportedly showing a benefit for prebiotics have said there is no benefit to infant health in adding prebiotics to infant formula.

The gastrointestinal tolerance of the test formula with 50% fermented milk and prebiotics was examined as part of the FIPS trial (Vandenplas et al, 2017) and this paper was also provided by Danone Nutricia as evidence that the new Aptamil formulations caused no adverse effects in infants. This study reported that infants fed a formula with 50% fermented milk and prebiotics experienced a lower incidence of colic (from parental report) at 4 weeks compared to infants fed formula containing only fermented milk, or only prebiotics. The same trial also reported (from parental report) that scores for flatulence were greater at 8 weeks in infants fed formula with 50% fermented milk and prebiotics compared to those fed formula with 15% fermented milk and prebiotics or formula with prebiotics only.

The LIFE trial reported equivalence in weight, length and head circumference gain between formula groups. Weight gain per day was reported as similar between the group fed formula with prebiotics (9:1) and 30% fermented milk and the breastfed reference group but not for the group fed standard formula and the breastfed reference group, who had a significantly higher weight gain per day. Both formula groups showed equivalence in length gain compared to the breastfed reference group. Head circumference gain was greater in both formula groups compared to the breastfed reference group. Overall the number of adverse events and serious adverse events did not differ between

formula fed groups. There were 31 adverse events in both groups, 12 of which were serious in the group fed formula with prebiotics and 30% fermented milk and 15 of which were serious in the group fed standard infant formula. There were 12 adverse events (38% of all adverse events) related to the study products. The number of participants who withdrew before completion of the study is not given (Rodriguez-Herrera et al, 2016a).

Stool characteristics were studied in further analysis of the LIFE data (but again we only have abstracts to consider). Rodriguez-Herrera abstracts reported that infants fed formula with prebiotics (9:1 GOS/FOS) and 30% fermented milk had significantly softer stools than infants fed with standard infant formula. Stool consistency was also reported to be closer to that of the breastfed reference group. Infants fed with prebiotics (9:1 GOS/FOS) and 30% fermented milk were also reported to have a higher median stool frequency from 9 weeks of age than infants fed a standard formula (Herrera et al, 2015). Infants fed with formula containing prebiotic and 30% fermented milk were also reported to have a significantly higher probability of having soft stools and a significantly lower probability of having hard stools than infants fed with standard infant formula (Rodriguez-Herrera et al, 2016b).

A further abstract provided by Danone Nutricia in support of their product relates only to the probability of breastfed infants having a soft stool consistency. This analysis reported that breastfed infants were more likely to have soft pudding like stools than any other stool consistency (Rodriguez-Herrera et al, 2016c).

Questions for Danone Nutricia

Q11. In the FIPS study, was analysis of formula toleration conducted on the intention to treat or per protocol population?

Q12. If the FIPS and LIFE trials test formula are different to the Aptamil infant formula currently marketed in the UK, how can this trial data be used to justify safety and efficacy statements?

Q13: How do the clinical advantages of fermented milk plus prebiotics differ to those previously claimed by Danone Nutricia for the addition of prebiotics to infant formula without fermented milk?

References

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