



## Danone Nutricia Aptamil infant milk reformulation update.

October 2018

### Key points

Aptamil infant, follow-on and growing up milk powders and Aptamil infant 70ml ready to feed (RTF) contain 26% fermented milk.

The fermentation process uses the probiotic bacteria *Bifidobacterium breve* and *Streptococcus thermophiles* strains as processing aids. Although live bacteria are not present in the final product, metabolites from the fermentation process are present but information on what these are has not been provided.

One of the two main clinical trials on which claims for the safety and efficacy of the products are based has not been published in a peer reviewed journal.

Claims that the current formulation has been tested on 1500 babies are based on clinical trials conducted since 1994 on any fermented formula milk, none of which appear to be equivalent in terms of nutritional composition or percentage of fermented product used, to the current formulations.

Expert opinion and systematic review state that there are no clear benefits for the addition of either prebiotics or fermented milk to standard infant formula (EFSA, 2014; Agostoni et al, 2007; Szajewska et al, 2016).

Danone Nutricia have stated that they do not wish to 'mislead an average consumer regarding the health benefits of the partially fermented product' and so do not include information on product labels that fermented milk has been added. They do however continue to make statements about the benefits of the new formulation in print and on their website, which we do not believe are supported by the evidence provided.

### 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. In July 2018 we produced a statement outlining what we knew about the product changes at that time. In response to our initial request for information, Danone provided us with a list of references as evidence of the safety and efficacy of their reformulated products. These related to two studies - the FIPS Study and the LIFE study. In September 2018 we released a further statement which updated what we had learned about the process used and assessed the evidence provided by Danone Nutricia about the safety and efficacy testing of the

products. We also posed some questions about the evidence base and the product composition. We have now received a response from Danone Nutricia that answers some, but not all of our questions. This statement updates our current knowledge with what we have learnt from Danone and highlights questions that remain unanswered.

### **Which formulations have changed?**

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, however, it is now apparent that the formulation of the 70ml Ready to Feed (RTF) first infant formula milk has also changed. Please note that at the time of writing, the Danone Nutricia website for healthcare professionals indicates on the product page that only the powdered formulations have changed.

### **Compositional changes to Aptamil formula milks**

Danone Nutricia have said that changes have been made to the process used to make the milk rather than to the formulation itself, however, the datacards show differences in the proportions of ingredients used to make the reformulated product. 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.

### **Processing changes to Aptamil infant milks: what more do we know about 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 evidence base provided by Danone suggests that it is this process that is used in the manufacture of their reformulated Aptamil brand products in the UK. Danone Nutricia have confirmed that 26% of the milk used in the reformulated products is milk fermented using their 'unique process'.

The probiotic bacteria *Bifidobacterium breve* & *Streptococcus thermophiles* are used in the fermentation process, however the patented process known as Lactofidus™ is not used in the UK marketing of the product. The process leaves no viable bacteria in the final product, but their metabolites are present. We have not been provided with any further details of the process including the nature of the metabolites now present in the reformulated milks as a result of the fermentation process, the thermal treatment used to deactivate the live bacteria or the quality control procedures used

to ensure that the product no longer contains live bacteria. Danone Nutricia have, however, said that they have standardised the process with strict quality criteria and are confident that the metabolite types and levels are the same with every production. It should therefore be possible to provide information to consumers on what these metabolites are as they are obviously testing for the presence of these.

### **Why do Danone Nutricia not make it clear on the packaging that the milk has been fermented and contains bioactive fermentation products?**

Danone Nutricia have not made it clear on the packaging or the product pages of their website that the reformulated products contain 26% fermented milk and fermentation metabolites. When asked why they have not done this, Danone Nutricia have said that they do not wish to state that the product is partially fermented as this could suggest a health benefit and that they use descriptive language such as '*our unique process*' without mentioning fermentation so as '*not to mislead an average consumer regarding the health benefits of the partially fermented product*'.

It is interesting therefore that that 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 and that when asked about any clinical advantages of fermented milk with prebiotics Danone Nutricia replied that:

*'The combination of our new unique process and (9:1 GOS/FOS) blend provides beneficial effects closer to human-fed infants. This includes:*

*Microbiota composition and faecal metabolite profile;  
Stool consistency;  
More frequent stools'*

The references given to support some of these claims in advertising for Aptamil follow-on formula is from poster and oral presentations at a conference and not from peer reviewed journal papers.

### **Have all the clinical trials used to support safety and efficacy claims been published in peer reviewed journals?**

Danone Nutricia provided us with a list of references from two clinical trials the LIFE study and the FIPS study to support their claims that the milks had been subject to extensive clinical trials. In our September 2018 statement we highlighted that one of these studies did not appear to have been published in a peer reviewed journal and the evidence provided was from poster presentations and abstracts. Danone Nutricia have confirmed that this study has not yet been published in a peer reviewed journal but that the manuscript has been submitted for peer review.

The specific questions we asked about the evidence base and 'unique process' used in the manufacture of the reformulated products together with Danone Nutricia's response are outlined below.

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

*'the LIFE manuscript has been submitted for peer review'*

**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?**

*".. we use the *Bifidobacterium breve* & *Streptococcus thermophiles* strains as a processing aid. The UK formulation is based on 26% (including the RFT 70ml) fermented milk with (9:1 GOS/FOS)."*

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

Metabolites deriving from fermentation are highly complex in composition. We have standardised the process with strict quality criteria and therefore we are confident that the metabolites types and levels are the same with every production.

**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?**

*'the fermentation process which you refer to is only a partial fermentation of the product... It may be misleading to proclaim the product is partially fermented, because, among other things, calling attention to the partial fermentation could suggest a health benefit.... We use descriptive language such as 'our unique process' without mentioning that one part of the product has been fermented so as not to mislead an average consumer regarding the health benefits of the partially fermented product'*

**What do we know about the test formulas and the number of babies included in clinical trials of the new formulation?**

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

in the clinical trials that we are aware of is much lower than 1500 and the formulas tested in the clinical trials contained 15%, 30% or 50% fermented milk, with or without prebiotics. Furthermore, the test products used in the clinical trials do not appear to have the same nutritional composition as that of the product currently marketed in the UK.

When asked about the test formulas and the number of infants included in trials of the current Aptamil formulation, Danone Nutricia have indicated that they have been conducting clinical trials on formula milks containing fermented milk since 1994 and that 1500 babies have been included in these trials. It is still not clear whether any babies have been included in clinical trials of the current Aptamil formulation containing 26% fermented milk.

The specific questions we asked about the clinical trials, the number of babies included in trials and the trial formula composition together with Danone Nutricia's response are outlined below.

**Q7. Which other trials are you including (apart from the FIPS and LIFE studies) when you say that the new formulation was tested on 1500 babies? Can you provide references for these studies?**

**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)?**

*The UK formulation is based on 26% (including the RFT 70ml) fermented milk with (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?**

**Danone Nutricia did not specifically answer all of our questions but said in their response that:**

*"Our research into fermented product began in 1994 and since then we have continued to conduct further research, including on a total sample of 1,500 infants.*

## **What do the clinical trials tell us about the safety, tolerance and efficacy of formula milks with 26% fermented milk and prebiotics?**

We have provided a more comprehensive summary of the clinical trials included in Danone Nutricia's evidence base in our September 2018 statement than can be found at [www.firststepsnutrition.org/news/](http://www.firststepsnutrition.org/news/).

The FIPS study reported equivalence in weight gain across all groups which included babies fed formula with prebiotics and no fermented milk, prebiotics plus varying levels of prebiotics and milk with no prebiotics and a proportion of fermented milk. Tolerance was measured by parental report on the intention to treat population and all formulas were reported to be well tolerated despite a dropout rate of 36%, mainly due to an adverse event or the withdrawal of informed consent. 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 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 (Huet et al, 2016). The FIPS study also 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 (Vandenplas et al, 2017).

The LIFE trial, for which we only have abstracts and poster presentations, 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 was significantly higher for the group fed standard formula and the breastfed reference group. 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, 38% (12) of which were related to the study products (Rodriguez-Herrera et al, 2016).

Further analysis of the LIFE data reported that infants fed formula with prebiotics (9:1 GOS/FOS) and 30% fermented milk had significantly softer stools and higher stool frequency than infants fed with standard infant formula. Stool consistency was also reported to be closer to that of the breastfed reference group (Herrera et al, 2015).

Given that the formula milks used in the clinical trials that we are aware of differ from the current Aptamil formulations, it is difficult to see how this data can be used to

justify claims for their safety and efficacy and statements that they have undergone extensive clinical trials. Danone Nutricia have not clarified how the clinical benefits previously claimed for the addition of prebiotics to their formula milks differ from those claimed for the addition of prebiotics and fermented milk. When we asked why evidence from the FIPS and LIFE trials were being used to justify claims made for the formula marketed in the UK, Danone Nutricia responded that:

*'All infant formulas which include our latest formulation are in-line with EU regulations and are therefore approved and safe for use in the EU'*

The specific questions we asked about use of this trial data to support statements around safety and efficacy and tolerance of formula milks with 26% fermented milk and prebiotics together with Danone Nutricia's response are outlined below.

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

*'The analyses of tolerance parameters (GI symptoms, crying, sleeping and stool characteristics) were performed on the intention to treat population. The analysis of safety was performed on the all subjects treated 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?**

*'All infant formulas which include our latest formulation are in-line with EU regulations and are therefore approved and safe for use in the EU'*

**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?**

*'The combination of our new unique process and (9:1 GOS/FOS) blend provides beneficial effects closer to human-fed infants. This includes:  
Microbiota composition and faecal metabolite profile;  
Stool consistency;  
More frequent stools'*

**What does expert opinion say about the current evidence for benefit associated with adding prebiotics to infant formula, or for fermented formula?**

The European Food Safety Authority (EFSA, 2014) and the EFSA panel considering health claims, have concluded that there is no evidence for health benefits from the addition of prebiotic oligosaccharides to infant or follow-on formula.

Despite widespread use in other European countries such as France and in African countries, there is little published data available to support the use of fermented 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.

Despite this expert opinion and Danone Nutricia's stated intention not to mislead consumers about the health benefits of partially fermented formula with prebiotics, they continue to make statements on their website and in advertisements in health professional journals suggesting that the new formulations provide beneficial effects.

The Aptamil website product page states that:

*Now combined with our unique process to produce postbiotics, which have been shown to support gut and immune markers closer to breastfed infants*

*Now, Aptamil powder formulations undergo Nutricia's unique process, producing postbiotics.*

*This combination of prebiotics and postbiotics have been shown to support a healthy gut in infants, important for immune system development and functioning.*

## **References**

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