

Author's response to reviews

Title: The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized cross-over trial.

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Version: 2 Date: 19 March 2007

Author's response to reviews: see over

Date: 19 march, 2007

Re: resubmission manuscript entitled “The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized cross-over trial.”

Dear Editor:

Hereby we resubmit the manuscript, “The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized cross-over trial.” Thank you for your interest in publishing this paper in *Nutrition Journal*.

The recommendations of the reviewers were valuable and therefore we have made modifications to the manuscript. Please find attached to this letter our response to the comments of the reviewers.

Sincerely,

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Response to comments of the reviewers on the submitted article “*The clinical effect of a new infant formula in term infants with constipation: a double-blind, randomized cross-over trial*”

Reviewer 1:

1. As supposed by the reviewer we gave more information on the proportion of palmitic acid at the sn-2 position in the formulas (see table 1). Furthermore, we have made some changes in the introduction, in the paragraph concerning the structure of triglycerides with regards to palmitic acid to be more clear about the difference between human milk and infant formulas (see page 3).
2. We agree with the reviewer on this point. Therefore we included in the abstract that this new formula also contains hydrolyzed whey protein and may also have played a role in influencing stool consistency.

Reviewer 2:

1. As suggested by the reviewer we discussed the remark that hydrolyzed proteins might be responsible for the increase in defecation frequency for both NF and SF groups in the discussion section on page 10.
2. We agree on the fact that a too small sample size in this study possible has influence the assessment of the effects of this new infant formula. The reviewer cited the study by Alarcon et al. on gastrointestinal tolerance of a new infant milk formula as an example for our study. However, this was an open-labeled, observational study. As this study design is more prone to bias from both the investigators and the participating parents with their infants, a larger sample size is necessary. Furthermore, Alarcon et al. compared five feeding regimens with differences in the number of subjects per group, which also requires a far larger sample size. This study therefore can not be compared in sample size with our double-blind randomized control trial comparing two feeding regimens.
To address the issue of sample size and power of our study, we have added in the *method section* on statistical analysis the power calculation conducted prior to the start of the study (see page 5). Furthermore, we included considerations about sample size and power of the study in the *discussion section* regarding the interpretation of study outcome (see page 10-11).
3. We did not collect information regarding the long-term effects and cost-effectiveness during this study, and therefore can not answer these questions.

Reviewer 3:

1. The confidence intervals mentioned in the abstract, results and table 3 are not all related to relative risks. Since this was not properly clarified in the text, we have added to the mentioned 95% CI the difference between means in case of continuous outcomes and the Relative Risk related in case of categorical endpoints.
2. As stated by the reviewer, we found a Relative Risk of 1.80 with a corresponding 95% confidence interval of 0.94-3.46 (see abstract and page 7). The RR expresses the association between the type of feeding formula and the occurrence of change from hard to soft stools. If the 95% CI of the RR includes a value of 1, you cannot assume that the factor is associated with the event. A value of 1 for RR means that there is equal risk for the event for both feeding formulas. This accompanying 95%CI includes the value of 1 and the minimum of the range is even below 1 (0.94), meaning that there is the possibility that the RR is correlated the other way around. So it is correct that statistical analysis revealed no statistical significance ($p=0.14$).

Other changes:

- page 3: We have corrected here that we received the formula from Numico Research, Wageningen, The Netherlands, but a grant for Nutricia BV, Zoetermeer, The Netherlands (see page 12).

- page 5: We have further specified that both the parents and the physicians were blind to randomization the entire study, to exclude any thought that drop-out was influenced by bias.

- page 6: We have conducted a more specific analysis of change in defecation frequency between the two formulas during period 1. Instead of Student's t-test, an ANCOVA was calculated (see page 6), as this analysis includes baseline defecation frequency for each individual. This is a more sensitive analysis, but outcome did not change. Results of this analysis are given on page 7, in table 3 and in the abstract section.

- The notation of the mixture of GOS/FOS used in the new formula has recently been adjusted and is now notated as GOS/lcFOS (lc stands for long chain). We have implemented this notation throughout the text.