

April 28, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 20140428_Manuscript_WJG_revise).

Title: Stool characteristics of infants receiving short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides: a review

Author: Petra AMJ Scholtens, Dominique AM Goossens, Annamaria Staiano.

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 9457

We are grateful for the positive remarks about our manuscript and we would like to thank you for the opportunity to adjust the manuscript with the specific remarks that were made by both reviewers. We have made adjustments throughout the manuscript (marked in yellow). For some specific comments to the two reviewers, we have replied to the remarks below.

We hope that these adjustments will fulfil the remarks and we look forward to your response.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

Petra Scholtens

Reviewer 1

The specific comments (as listed below) have been adjusted throughout the manuscript.

1. Page 3, line 13 and throughout manuscript - Avoid use of the word "parameters" in this context as its strict meaning has to do with statistical matters. Rather, use "outcomes" or "characteristics" instead.
2. Page 8, line 14 - ...Veereman-Wauters et al., a ...
3. Page 8, line 24 - Bisceglia et al followed ...
4. Page 9, line 20 - What are the units for viscosity, centipoise?
5. Page 10, line 5 - stools
6. Page 10, line 7 - ... groups, respectively, was ...
7. Page 10, line 9 - ... groups, respectively ...
8. Page 11, lines 5 and 6 - Change "levels" to "concentrations".
9. Page 11, line 6 - How much increase is noted in concentrations of bifido and lacto genera? What percentage of the microbes in the colon of the infant do these constitute?
10. Page 11, line 13 - ... have indeed been shown ...
11. Page 11, line 21 - 0.8 g/L
12. Page 11, lines 23 and 24 - Quantify these responses. In some occurrences, studies have been mentioned more than once. We quantified the responses only on the first occurrence.
13. Page 11, line 28 - ... observed in human milk-fed infants.
14. Page 12, line 1 - Remove "the".
15. Page 12, line 4 - ... in a ratio of 9:1.
16. Page 12, lines 5-6 - Expand on this point. HMO's are very complex and it's difficult for me to understand how a simple mixture of GalOS and Inulin could simulate in any way their structure. Please provide some explanatory language here.
17. Page 12, line 16 - ... Russo et al. indicated ...
18. Page 12, line 20 - Quantify this response. In some occurrences, studies have been mentioned more than once. We quantified the responses only on the first occurrence.
19. Page 19, Figure 1 - What is the title of this figure? Also, the format is very difficult to understand. Consider re-formatting to increase the clarity of the message that you are trying to convey in the use of this figure.

With respect to the general comments, please find our response below.

20. This is a well written review of a very specific topic, namely, the effects on stool characteristics of a ratio of 9 GalOS:1 long chain fructooligosaccharides. Authors have summarized the work that has been conducted on this topic.

21. In addition to the suggestions listed previously, authors should consider the following in preparation of the next draft of their paper:

- 1. What does the literature say about supplying these two oligosaccharides separately in infant formula? Those studies should be summarized and reported here. Multiple studies have been done with different types of oligosaccharides, such as for instance galacto-oligosaccharides, fructo-oligosaccharides and inulin, pectin hydrolysates, polydextrose. An overview of the effects of all types of oligosaccharides is beyond the scope of our manuscript, and we aimed to focus only on the mixture of galacto-oligosaccharides and fructo-oligosaccharides in a ratio of 9:1.
- 2. What sources of GalOS and long chain fructooligosaccharides were used? That information should be listed for each study reviewed. Also, the purity of the OS should be reported. Most of the studies do not specifically mention the source and purity of the scGOS and lcFOS. However, in the study of Moro *et al* (2002) and Boehm *et al.* (2002), it is mentioned that the scGOS is derived from lactose and the lcFOS is inulin extracted from chicory root. We added that information to the manuscript.
- 3. Some information should be included as to the viability of the OS after they have undergone processing to manufacture the baby formula. Is there any loss in prebiotic efficacy? The oligosaccharides that are used in the studies have all been processed during the manufacture of the infant formula. The same is true for the formulas in the studies in which the prebiotic effects of these oligosaccharides were investigated, so we cannot compare the difference between the processed oligosaccharides in the infant milk formulas and the unprocessed oligosaccharides.

Reviewer 2:

The adjustments that are mentioned below have been applied throughout the manuscript.

The review submitted by Scholtens and co-authors addressed the effect of a specific and industrially consolidated mixture of scGOS/lcFOS (9:1) on gut transit time, stool consistency and frequency in term and preterm infants. The review is well-written, contains useful information, is clear and concise and includes relevant bibliographic information. In my opinion, this manuscript is relevant enough to be published in the World Journal of Gastroenterology.

I have only some minor questions to be addressed before potential publication.

- 1.- First paragraph, page 6. In addition to affect sodium and water absorption, SCFA production following prebiotics fermentation has also an impact on mineral absorption (mainly, calcium and magnesium). The authors could include some comment on this subject in the revised version of the manuscript. *We added a sentence in which this is mentioned.*
- 2.- First paragraph, page 8. In the body text is indicated that the study of Moro et al. was performed with 0.8g/100 mL of scGOS/lcFOS whereas in Figure 1 a dose of 0.4/0.8g/100 ml is indicated. Please, clarify this point. *We adjusted this in the Figure/Table.*
- 3.- Second paragraph, page 11. Please, could the authors be more specific on the production of SCFA provided by the ingestion of infant milk formulas with scGOS/lcFOS?. I mean, which type of SCFA has been described to be produced/increased (butyrate, acetate, propionate, formic, lactate)? all of them?. *We have elaborated a bit more on the types and amounts of SCFA that are produced in the revised version.*
- 4.- Conclusion section. Please correct the spelling mistake "lCOS" (I guess it should be "lcFOS"). *Yes, we have adjusted this.*
- 5.- Figure 1. Please use decimal points instead of comma. *We have adjusted this.*