Statement on the safety of lacto-N-neotetraose and 2'-O-fucosyllactose as novel food ingredients in food supplements for children

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)

Published in:
E F S A Journal

DOI:
10.2903/j.efsa.2015.4299

Publication date:
2015

Document version
Publisher's PDF, also known as Version of record

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 28 October 2015

PUBLISHED: 13 November 2015

doi:10.2903/j.efsa.2015.4299

Statement on the safety of lacto-*N*-neotetraose and 2'-*O*-fucosyllactose as novel food ingredients in food supplements for children

EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)

Abstract

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to provide a scientific opinion on the safety of lacto-*N*-neotetraose and 2'-*O*-fucosyllactose as novel food ingredients in food supplements for children (excluding infants). In July 2015, the Panel concluded that LNnT and 2'-FL are safe for infants and for young children when added to infant, follow-on and young-child formulae under specific conditions of use; and for adults when added to foods at the uses and use levels proposed by the applicant, which include food supplements at a maximum intended daily intake of 1.5 g for LNnT and 3 g for 2'-FL. The applicant also intends to include LNnT and 2'-FL in food supplements for children, with maximum daily intake levels of 0.6 g for LNnT and 1.2 g for 2'-FL for toddlers (1–3 years of age), and maximum daily intake levels of 1.5 g for LNnT and 3 g for 2'-FL for children (4–18 years of age). In this scientific assessment, maximum daily intakes from food supplements for toddlers, children and teenagers are presented and two scenarios are calculated in which the maximum daily intakes from food supplements are added to the mean and 95th percentile intake estimates from all foods in which LNnT and 2'-FL are intended to be added. The Panel concludes that LNnT and 2'-FL are safe for the proposed use in food supplements at the maximum use levels proposed for toddlers (1–3 years of age) of 0.6 g/day for LNnT and 1.2 g/day for 2'-FL (alone or in combination) and for children (4-18 years of age) of 1.5 g for LNnT and 3 g for 2'-FL (alone or in combination). However, in children of 1-10 years of age the combined intakes from all foods in which the NFIs are intended to be added and from food supplements could result in intake levels which were reported to cause mild gastrointestinal symptoms in adults.

Keywords: lacto-*N*-neotetraose, 2'-*O*-fucosyllactose, food supplements, novel foods

Requestor: European Commission

Question numbers: EFSA-Q-2015-00594, EFSA-Q-2015-00595

Correspondence: nda@efsa.europa.eu

Panel members: Jean Louis Bresson, Barbara Burlingame, Tara Dean, Susan Fairweather-Tait, Marina Heinonen, Karen Ildico Hirsch-Ernst, Inge Mangelsdorf, Harry McArdle, Androniki Naska, Monika Neuhäuser-Berthold, Grażyna Nowicka, Kristina Pentieva, Yolanda Sanz, Alfonso Siani, Anders Sjödin, Martin Stern, Daniel Tomé, Dominique Turck, Hendrik Van Loveren, Marco Vinceti and Peter Willatts.

Acknowledgements: The Panel wishes to thank the members of the Working Group on Novel Foods: Tara Dean, Karl-Heinz Engel, Marina Heinonen, Inge Mangelsdorf, Rosangela Marchelli, Harry McArdle, Monika Neuhäuser-Berthold, Annette Pöting, Morten Poulsen, Yolanda Sanz, Josef Schlatter and Hendrik van Loveren for the support provided to this scientific output.

Suggested citation: EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2015. Statement on the safety of lacto-*N*-neotetraose and 2'-*O*-fucosyllactose as novel food ingredients in food supplements for children. EFSA Journal 2015;13(11):4299, 11 pp. doi:10.2903/j.efsa.2015.4299

ISSN: 1831-4732

The EFSA Journal is a publication of the European Food Safety Authority, an agency of the European Union.

Summary

Following a request from the European Commission, the Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to provide a scientific opinion on the safety of lacto-*N*-neotetraose and 2'-*O*-fucosyllactose as novel food ingredients (NFIs) in food supplements for children (excluding infants).

In July 2015, the Panel concluded that LNnT and 2′-FL are safe for infants and for young children when added to infant, follow-on and young-child formulae under specific conditions of use; and for adults when added to foods at the uses and use levels proposed by the applicant, which include food supplements at a maximum intended daily intake of 1.5 g for LNnT and 3 g for 2′-FL.

The applicant also intends to include LNnT and 2′-FL in food supplements for children, with maximum daily intake levels of 0.6 g for LNnT and 1.2 g for 2′-FL for toddlers (1-3 years of age), and maximum daily intake levels of 1.5 g for LNnT and 3 g for 2′-FL for children (4-10 years of age) and teenagers (11-18 years of age).

In this scientific assessment, maximum daily intakes from food supplements for toddlers, children and teenagers are presented and two scenarios for each population group are calculated in which the maximum daily intakes from food supplements are added to the mean and 95th percentile intake estimates (on a per kg body weight basis) from all foods in which LNnT and 2′-FL are intended to be added.

For children at the considered age from 1 to 18 years, daily intakes from food supplements at the proposed maximum levels would be below the 95th percentile daily intakes estimated for LNnT and 2′FL from all proposed foods intended to contain these NFIs, which were already considered safe by the Panel in July 2015.

In children of 1–10 years of age the combined intakes from all proposed foods, which are intended to contain the NFI, plus food supplements, could result in intake levels which were reported to cause mild gastrointestinal symptoms in adults.

However, the Panel notes that the intake estimates are based on the conservative assumptions that all proposed food items consumed by an individual actually contain the NFI at the maximum specified level of use and that in addition to such intakes these ingredients are also consumed from food supplements at the maximum proposed intake levels.

The Panel concludes that LNnT and 2′-FL are safe for the proposed use in food supplements at the maximum use levels proposed for toddlers (1–3 years of age) of 0.6 g/day for LNnT and 1.2 g/day for 2′-FL (alone or in combination) and for children (4–18 years of age) of 1.5 g for LNnT and 3 g for 2′-FL (alone or in combination).

However, in children of 1–10 years of age the combined intakes from all foods in which the NFIs are intended to be added and from food supplements could result in intake levels which were reported to cause mild gastrointestinal symptoms in adults.

Contents

1. Introduction

1.1. Background

In July 2015, EFSA published two Scientific Opinions on lacto-*N*-neotetraose and 2'-*O*-fucosyllactose as novel food ingredients (NFIs). Lacto-*N*-neotetraose (LNnT) and 2'-*O*-fucosyllactose (2'-FL) are synthetic oligosaccharides, which are intended to be used in infant and follow-on formulae, foods for special medical purposes for infants and young children and other foods for infants and young children, as well as in foods or food supplements for adults (EFSA NDA Panel, 2015a, b).

The Panel concluded that LNnT and 2'-FL are safe for infants (up to one year of age) when added to infant and follow-on formulae, in combination, at concentrations up to 0.6 g/L of LNnT and up to 1.2 g/L of 2'-FL, at a ratio of 1:2 in the reconstituted formulae; are safe for young children (older than one year of age) when added to follow-on and young-child formulae (alone or in combination), at concentrations up to 0.6 g/L of LNnT and up to 1.2 g/L of 2'-FL, at a ratio of 1:2. The Panel also concluded that LNnT and 2'-FL are safe when added to other foods at the uses and use levels proposed by the applicant, including food supplements for adults with a maximum intended daily intake of 1.5 g for LNnT and 3 g for 2'-FL.

The Panel considered that the maximum intended daily intake of 1.5 g for LNnT and 3 g for 2'-FL in food supplements for adults were safe, even if consumed on top of the estimated 95th percentile daily intake of LNnT (3.3 g) and 2'-FL (5 g) from all foods which are intended to contain these ingredients. The Panel noted that the intake estimate is based on the conservative assumption that all proposed food items consumed by an individual actually contain the NFI at the maximum specified level of use. The conclusion on safety was substantiated by the results of a randomised clinical trial in healthy adults over two weeks which showed that once per day intakes of 5 g of LNnT or 10 g of 2'-FL were not associated with any undesirable effects (Unpublished study report, 2015; EFSA NDA Panel, 2015a, b). Intakes of 5 g of LNnT and 10 g of 2'-FL per day correspond to 71 and 143 mg/kg body weight (bw), respectively, considering 70 kg as default value for the bw of adults. At the end of the intervention, a significantly higher incidence of passing gas was reported by participants who consumed daily either 10 g or 20 g (286 mg/kg bw) of LNnT compared with the placebo group. For 2'-FL, a significantly higher incidence of nausea, rumbling, bloating, passing gas, diarrhoea, loose stools and urgency was reported for participants who consumed daily the highest studied dose of 20 g of 2'-FL when compared with the placebo group. Stool consistency scores on the Bristol Stool scale were not significantly different between the intervention and placebo groups. All adverse events were reported to be 'mild'.

1.2. Terms of Reference as provided by the requestor

Since the EFSA opinions have considered the intended use of LNnT and 2'-FL in food supplements only for adults, the Commission requested EFSA to assess the safety of these novel food ingredients in food supplements also for children (excluding infants).

2. Data and Methodologies

2.1. Data

The assessment of the safety of lacto-*N*-neotetraose and 2'-*O*-fucosyllactose consumed in food supplements for children is based on the scientific opinions on the safety of lacto-*N*-neotetraose and 2'-*O*-fucosyllactose as novel food ingredients pursuant to Regulation (EC) No 258/97, the documentation provided to EFSA as indicated in those scientific opinions, and a letter provided by the applicant on 5 October 2015 as part of the mandate.

2.2. Methodologies

The assessment follows the methodology set out in Commission Recommendation 97/618/EC of 29 July 1997 concerning the scientific aspects and the presentation of information necessary to support applications for the placing on the market of novel foods and novel food ingredients and the

preparation of initial assessment reports under Regulation (EC) No 258/97 of the European Parliament and of the Council.

3. Assessment

In the information provided to EFSA, the applicant proposes 0.6 g/day of LNnT and 1.2 g/day of 2'-FL as the maximum daily intake levels from food supplements for toddlers (1–3 years of age). For children aged 4–10 years and teenagers (11–18 years of age) the same maximum daily intakes as intended for adults, i.e. 1.5 g for LNnT and 3 g for 2'-FL, were proposed.

The intake estimate provided by the applicant was based on the estimates as presented in the two EFSA Opinions (EFSA NDA Panel, 2015a, b), taking into account additional intakes from food supplements for children aged 1–18 years.

Table 1 and 2 provide figures from mean and 95th percentile intake estimates on a per kg bw basis for LNnT and 2'-FL based on UK national diet and nutrition survey (NDNS) consumption data and the use levels in foods as proposed by the applicant. In addition to these figures, which were already assessed and presented in the EFSA Opinions of 2015 (EFSA NDA Panel, 2015a, b), additional maximum intakes from food supplements are presented and two scenarios are calculated in which the maximum intakes from food supplements are added to the total intake (i.e. mean and 95th percentile intake estimates) from the proposed food categories for these two ingredients.

3.1. Toddlers (1–3 years of age)

The maximum daily use levels intended by the applicant for food supplements for toddlers are 0.6 g for LNnT and 1.2 g for 2'-FL.

3.1.1. Lacto-*N*-neotetraose

In its Opinion on LNnT (EFSA NDA Panel, 2015a), the Panel considered that the estimated 95th percentile intake of LNnT for toddlers from the proposed food categories (132 mg/kg bw per day) was significantly below the estimated 95th percentile intake (330 mg/kg bw per day) for infants aged 4-6 months based on UK NDNS consumption data. At the proposed maximum daily intake levels, food supplements could provide additional intakes of about 42 mg LNnT per kg bw for toddlers. The addition of the proposed maximum daily intake levels from food supplements to the mean and the 95th percentile intake of LNnT from the proposed food categories would result in 105 and 175 mg/kg bw per day, respectively. The 95th percentile intake from the proposed food categories plus food supplements (175 mg/kg bw per day) would result in intakes of about half of the estimated 95th percentile daily intake for infants. The Panel notes that the 95th percentile intake from the proposed food categories plus food supplements (175 mg/kg bw per day) is moderately above the dose level (143 mg/kg bw per day) for which a study in healthy adult subjects reported a higher incidence of passing gas as compared with the placebo group (Unpublished study report, 2015; EFSA NDA Panel, 2015a).

3.1.2. 2'-*O*-fucosyllactose

In its Opinion on 2'-FL (EFSA NDA Panel, 2015b), the Panel considered the estimated 95th percentile intake of 2'-FL for toddlers from the proposed food categories (247 mg/kg bw per day) and the 95th percentile intake (209 mg/kg bw per day) for a 3-months old infant, based on consumption data from the EFSA Comprehensive Food Consumption Database. At the proposed maximum daily intake levels, food supplements could provide additional intakes of about 86 mg of 2'-FL per kg bw for toddlers. The addition of the proposed maximum daily intake levels from food supplements to the mean and the 95th percentile intake of 2'-FL from the proposed food categories would result in 206 and 333 mg/kg bw per day, respectively. The 95th percentile intake from the proposed food categories plus food supplements (333 mg/kg bw per day) would be around 60% above the 95th percentile intake for a 3-months old infant, based on consumption data from the EFSA Comprehensive Food Consumption Database (209 mg/kg bw per day). The Panel notes that the 95th percentile intake from the proposed food categories plus food supplements (333 mg/kg bw per day) is moderately above the dose level (286 mg/kg bw per day) for which a study in healthy adult subjects reported a higher incidence of

nausea, rumbling, bloating, passing gas, diarrhoea, loose stools and urgency as compared with the placebo group (Unpublished study report, 2015; EFSA NDA Panel, 2015b).

3.2. Children (4–10 years of age)

The maximum daily use levels intended by the applicant for food supplements for children are 1.5 g for LNnT and 3 g for 2'-FL.

3.2.1. Lacto-*N*-neotetraose

Food supplements could provide an additional 60 mg of LNnT per kg bw per day on top of the estimated mean (31 mg) and the 95th percentile (72 mg) daily intakes from the proposed food categories, which could result in intakes of about 91 or 132 mg per kg bw, respectively. The Panel notes that the 95th percentile intake from the proposed food categories plus food supplements (132 mg/kg bw per day) is close to the dose level (143 mg/kg bw per day) for which a study in healthy adult subjects reported a higher incidence of passing gas as compared with the placebo group (Unpublished study report, 2015; EFSA NDA Panel, 2015a).

3.2.2. 2'-*O*-fucosyllactose

Food supplements could provide an additional 120 mg of 2'-FL per kg bw per day on top of the estimated mean (58 mg) and the 95th percentile (135 mg) daily intakes from the proposed food categories, which could result in intakes of about 178 or 255 mg per kg bw, respectively. The Panel notes that the 95th percentile intake from the proposed food categories plus food supplements (255 mg/kg bw per day) is close to the dose level (286 mg/kg bw per day) for which a study in healthy adult subjects reported a higher incidence of nausea, rumbling, bloating, passing gas, diarrhoea, loose stools and urgency as compared with the placebo group (Unpublished study report, 2015; EFSA NDA Panel, 2015b).

3.3. Teenagers (11–18 years of age)

The maximum daily use levels intended by the applicant for food supplements for teenagers are 1.5 g for LNnT and 3 g for 2'-FL.

3.3.1. Lacto-*N*-neotetraose

Food supplements could provide an additional 26 mg of LNnT per kg bw per day on top of the estimated mean (13 mg) and the 95th percentile (35 mg) daily intakes from the proposed food categories, which could result in intakes of about 39 and 61 mg per kg bw per day, respectively. The Panel notes that these estimates are below the dose level (71 mg per kg bw per day) which was not associated with undesirable effects in a study in healthy adults and about half of the dose level (143 mg per kg bw per day) for which a statistically significant higher incidence of passing gas was reported as compared with the placebo group (Unpublished study report, 2015; EFSA NDA Panel, 2015a).

3.3.2. 2'-*O*-fucosyllactose

Food supplements could provide an additional 53 mg of 2'-FL per kg bw per day on top of the estimated mean (23 mg) and the 95th percentile (55 mg) daily intakes from the proposed food categories, which could result in intakes of about 76 or 108 mg per kg bw per day, respectively. The Panel notes that these estimates are below the dose level (143 mg per kg bw per day) which was not associated with undesirable effects in a study in healthy adults and about one third of the dose level (286 mg per kg bw per day) for which a statistically significant higher incidence of nausea, rumbling, bloating, passing gas, diarrhoea, loose stools and urgency was reported as compared with the placebo group (Unpublished study report, 2015; EFSA NDA Panel, 2015b).

Table 1: Summary of the estimated daily per kg bw intake of LNnT from proposed food categories and food supplements by different population groups in the UK, based on data from NDNS

Population groups	Age group (years)	All-user consumption (mg/kg bw per day)					
		n	Mean from proposed food categories	95th percentile from proposed food categories	Maximum proposed intakes from supplements	Mean from proposed foods PLUS maximum food supplements	95th percentile from proposed foods PLUS maximum food supplements
Toddlers	1–3	219	63	132	42	105	175
Children	4–10	423	31	72	60	91	132
Teenagers	11–18	451	13	35	26	39	61
Women of child-bearing age	19–40	216	13	53	23	36	76
Female adults	19–64	460	13	40	26	39	66

Table 2: Summary of the estimated daily per kg bw intake of 2'-FL from proposed food categories and food supplements by different population groups in the UK, based on data from NDNS

Population groups	Age group (years)	All-user consumption (mg/kg bw per day)					
		n	Mean from proposed food categories	95th percentile from proposed food categories	Maximum proposed intakes from supplements	Mean from proposed foods PLUS maximum food supplements	95th percentile from proposed foods PLUS maximum food supplements
Toddlers	1–3	219	120	247	86	206	333
Children	4–10	423	58	135	120	178	255
Teenagers	11–18	451	23	55	53	76	108
Women of child-bearing age	19–40	216	24	75	45	69	120
Female adults	19–64	460	28	74	52	80	126

4. Discussion

For children at the considered age from 1 to 18 years, daily intakes from food supplements at the proposed maximum levels would be below the 95th percentile daily intakes estimated for LNnT and 2'FL from all proposed foods intended to contain these NFIs, which were considered safe in the previous EFSA Opinions (EFSA NDA Panel, 2015a, b).

For toddlers, adding the maximum proposed daily intakes from food supplements to the 95th percentile intakes from all proposed food categories considered in the EFSA Opinions on LNnT and 2'-FL (EFSA NDA Panel, 2015a, b) would result in intakes of about half of the estimated 95th percentile daily intake for infants for LNnT (330 mg/kg bw) and around 60% above the estimated 95th percentile daily intake for infants for 2'-FL (209 mg/kg bw), as considered in these EFSA Opinions.

In children of 1-10 years of age such combined intakes from all proposed foods which are intended to contain the NFI plus food supplements, could result in intake levels (on a per kg body weight basis) which were reported to cause mild gastrointestinal symptoms in adults such as nausea, rumbling, bloating, passing gas, diarrhoea, loose stools and urgency. Since no human study has been provided on children other than infants, no conclusion can be made as to whether or at which dose levels children at this age would experience such symptoms.

However, the Panel notes that the intake estimates are based on the conservative assumptions that all proposed food items consumed by an individual actually contain the NFI at the maximum specified level of use and that in addition to such intakes these ingredients are also consumed from food supplements at the maximum proposed intake levels.

5. Conclusions

The Panel concludes that LNnT and 2'-FL are safe for the proposed use in food supplements at the maximum use levels proposed for toddlers (1–3 years of age) of 0.6 g/day for LNnT and 1.2 g/day for 2'-FL (alone or in combination) and for children (4–18 years of age) of 1.5 g for LNnT and 3 g for 2'-FL (alone or in combination).

However, in children of 1–10 years of age the combined intakes from all foods in which the NFIs are intended to be added and from food supplements could result in intake levels which were reported to cause mild gastrointestinal symptoms in adults.

Documentation provided to EFSA

1. Letter from the European Commission to the European Food Safety Authority with the request for an assessment of the safety of 2'-*O*-fucosyllactose and lacto-*N*-neotetraose as novel food ingredients in food supplements for children. SANTE/E6/SS/ks D (2015) 4668784, dated 14 October 2015.

2. Letter from the applicant 'Novel Food Applications for 2'-*O*-fucosyllactose (2'-FL) and lacto-*N*-neotetraose (LNnT)' dated 28 September 2015 providing information on the proposed use level of the two ingredients in foods supplements and on estimated intakes. Submitted by Glycom A/S.

References

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2015a. Scientific opinion on the safety of lacto-*N*-neotetraose as a novel food ingredient pursuant to Regulation (EC) No 258/97. EFSA Journal 2015;13(7):4183, 32 pp. doi:10.2903/j.efsa.2015.4183

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2015b. Scientific opinion on the safety of 2'-*O*-fucosyllactose as a novel food ingredient pursuant to Regulation (EC) No 258/97. EFSA Journal 2015;13(7):4184, 32 pp. doi:10.2903/j.efsa.2015.4184

Unpublished study report, 2015. Dated: 1 June 2015. Study Title: 'The effects of human-milk-oligosaccharides on the faecal microbiota and on gastrointestinal symptoms in healthy adult volunteers' (Study number 2014-1).

Abbreviations

bw	body weight
2'-FL	2'-*O*-fucosyllactose
LNnT	lacto-*N*-neotetraose
NDNS	national diet and nutrition survey
NFI	novel food ingredient