Safety of the extension of use of 2'-fucosyllactose/difucosyllactose (2'-FL/DFL) mixture and lacto- N-tetraose (LNT) as novel foods in food supplements for infants pursuant to Regulation (EU) 2015/2283.

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Dominique Turck, T. Bohn, J. Castenmiller, S. de Henauw, K. I. Hirsch-Ernst, et al.. Safety of the extension of use of 2'-fucosyllactose/difucosyllactose (2'-FL/DFL) mixture and lacto- N-tetraose (LNT) as novel foods in food supplements for infants pursuant to Regulation (EU) 2015/2283.. EFSA Journal, 2022, EFSA Journal, 20, pp.e07140. 10.2903/j.efsa.2022.7140 . hal-04516205

HAL Id: hal-04516205
https://hal.univ-lille.fr/hal-04516205v1

Submitted on 22 Mar 2024

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SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 26 January 2022

doi: 10.2903/j.efsa.2022.7140

Safety of the extension of use of 2'-fucosyllactose/difucosyllactose (2'-FL/DFL) mixture and lacto-*N*-tetraose (LNT) as novel foods in food supplements for infants pursuant to Regulation (EU) 2015/2283

EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Dominique Turck, Torsten Bohn, Jacqueline Castenmiller, Stefaan De Henauw, Karen Ildico Hirsch-Ernst, Alexandre Maciuk, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Carmen Pelaez, Kristina Pentieva, Alfonso Siani, Frank Thies, Sophia Tsabouri, Marco Vinceti, Francesco Cubadda, Thomas Frenzel, Marina Heinonen, Rosangela Marchelli, Monika Neuhäuser-Berthold, Morten Poulsen, Miguel Prieto Maradona, Josef Rudolf Schlatter, Henk van Loveren, Paolo Colombo, Estefanía Noriega Fernández and Helle Katrine Knutsen

Abstract

Following a request from the European Commission, the EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA) was asked to deliver an opinion on the safety of the extensions of use of the authorised novel foods (NFs) 2'-fucosyllactose/difucosyllactose (2'-FL/DFL) mixture and lacto-*N*-tetraose (LNT) in food supplements (FS) for infants pursuant to Regulation (EU) 2015/2283. The NFs are produced by fermentation with genetically modified strains of *Escherichia coli* K-12 DH1 and already included in the EU list of NF. The applicant stated that no changes in the production process or the identity of the NFs occurred. The applicant proposes an extension of use of the NF containing 2'-FL/DFL mixture in FS intended for infants (< 1 year), at a maximum use level of 1.6 g/day for infants ≤ 6 months and up to 1.2 g/day for infants > 6 months. The applicant also proposes an extension of use of LNT in FS intended for infants (< 1 year), at a maximum use level of 0.8 g/day for infants ≤ 6 months and up to 0.6 g/day for infants > 6 months. The intake per kg body weight of 2'-FL/DFL and LNT from the proposed maximum use levels of the respective NFs in FS for infants does not exceed the lowest estimated mean intake of naturally occurring 2'-FL/DFL and it is similar to the highest estimated mean intake of LNT by breastfed infants. In addition, the Panel notes that the proposed uses of the NFs in FS for infants result in lower maximum daily intakes than those from the already authorised uses of the NFs for the same population group. The Panel concludes that the uses of the NFs containing either 2'-FL/DFL or LNT in FS for infants are safe under the proposed conditions of use.

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Keywords: 2'-fucosyllactose/difucosyllactose, lacto-*N*-tetraose, HiMO, Novel Foods, food supplement, extension of use, infants

Requestor: European Commission

Question numbers: EFSA-Q-2021-00090; EFSA-Q-2021-00091

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Panel members: Dominique Turck, Torsten Bohn, Jacqueline Castenmiller, Stefaan De Henauw, Karen Ildico Hirsch-Ernst, Helle Katrine Knutsen, Alexandre Maciuk, Inge Mangelsdorf, Harry J McArdle, Androniki Naska, Carmen Pelaez, Kristina Pentieva, Alfonso Siani, Frank Thies, Sophia Tsabouri and Marco Vinceti.

Declarations of interest: The declarations of interest of all scientific experts active in EFSA's work are available at https://ess.efsa.europa.eu/doi/doiweb/doisearch.

Suggested citation: EFSA NDA Panel (EFSA Panel on Nutrition, Novel Foods and Food Allergens), Turck D, Bohn T, Castenmiller J, De Henauw S, Hirsch-Ernst KI, Maciuk A, Mangelsdorf I, McArdle HJ, Naska A, Pelaez C, Pentieva K, Siani A, Thies F, Tsabouri S, Vinceti M, Cubadda F, Frenzel T, Heinonen M, Marchelli R, Neuhäuser-Berthold M, Poulsen M, Prieto Maradona M, Schlatter JR, Loveren HV, Colombo P, Noriega Fernández E and Knutsen HK, 2022. Scientific Opinion on the safety of the extension of use of 2'-fucosyllactose/difucosyllactose (2'-FL/DFL) mixture and lacto-*N*-tetraose (LNT) as novel foods in food supplements for infants pursuant to Regulation (EU) 2015/2283. EFSA Journal 2022;20(3):7140, 9 pp. https://doi.org/10.2903/j.efsa.2022.7140

ISSN: 1831-4732

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

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1. Introduction

1.1. Background and Terms of Reference as provided by the requestor

On 17 December 2019, the company Glycom A/S submitted a request to the European Commission in accordance with Article 10 of Regulation (EU) 2015/2283[1] to authorise the extension of use of the authorised novel food (NF) 2′-fucosyllactose/difucosyllactose mixture (2′- FL/DFL) in food supplements (FS) for infants. Also, on 17 December 2019, the same company submitted a separate request to the European Commission in accordance with Article 10 of Regulation (EU) 2015/2283 to authorise the extension of use of the authorised NF lacto-*N*-tetraose (LNT) in FS for infants.

The applicant has not requested data protection under Article 26 of Regulation (EU) 2015/2283 for neither the data in support of the request concerning 2′-FL/DFL nor for the data in support of the request concerning LNT.

In accordance with Article 10(3) of Regulation (EU) 2015/2283, the European Commission asks the European Food Safety Authority (EFSA) to provide a scientific opinion on the safety of the extension of use for each of the authorised NFs 2′-FL/DFL mixture and LNT to be used individually in FS for infants.

1.2. Interpretation of the Terms of Reference

The applications refer to an extension of use of the NFs 2′-FL/DFL mixture and LNT, whose respective use as NFs is already authorised in several food categories including: infant formulae (IF), follow-on formulae (FOF), milk-based drinks intended for young children (from 1 to < 3 years), processed cereal-based food and baby food for infants and young children and in FS for the general population, excluding infants. The applicant has now proposed to extend their use into FS for infants. Therefore, the current assessment is exclusively focussed on the proposed extensions of use with respect to the possible impact on the safety and nutritional aspects.

1.3. Additional information

2′-FL is included in the EU Union list of authorised NFs (Commission Implementing Regulation (EU) 2017/2470 of 20 December 2017[2]) when chemically synthesised or produced by fermentation with genetically modified strains of *Escherichia coli* K-12 and *E. coli* BL21. In 2015, EFSA published an opinion on the safety of the chemically synthesised 2′-FL as a NF (EFSA NDA Panel, 2015a) and a statement on its use in FS for children, excluding infants (EFSA NDA Panel, 2015b). In addition, a scientific opinion on the safety as a NF of the **2′-FL/DFL** mixture, produced by fermentation with a genetically modified strain of *E. coli* K-12 DH1, has also been published (EFSA NDA Panel, 2019a).

The NF containing the 2′-FL/DFL mixture (2′-FL/DFL ≥ 85% w/w dry matter (DM), with 2′-FL ≥ 75% and DFL ≥ 5% w/w DM) is authorised for use in FS for the general population, excluding infants (< 1 year), up to the maximum use level of 4 g/day.

LNT is included in the EU Union list of authorised NFs ((EU) 2017/2470[2]) when produced by fermentation with a genetically modified strain of *E. coli* K-12 DH1. A scientific opinion on the safety of LNT as a NF has been published in 2019 (EFSA NDA Panel, 2019b).

The NF containing LNT (LNT ≥ 70% w/w DM) is authorised for use in FS for the general population, excluding infants (< 1 year), up to the maximum dose of 2 g/day.

FS containing the NFs shall bear a statement that the corresponding FS should not be used if foods added with 2′-FL/DFL or LNT or human milk, are consumed on the same day.

2. Data and methodologies

2.1. Data

The safety assessment of these NFs is based on data supplied in the applications.

[1] Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) N0 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001 (2013/0435 (COD). OJ L 327, 11.12.2015, pp. 1–22.

[2] Commission Implementing Regulation (EU) 2017/2470 of 20 December 2017 establishing the Union list of novel foods inaccordance with Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. OJ L 351/72,30.12.2017.

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Administrative and scientific requirements for NF applications referred to in Article 10 of Regulation (EU) 2015/2283 are listed in the Commission Implementing Regulation (EU) 2017/2469[3].

A common and structured format on the presentation of NF applications is described in the EFSA guidance on the preparation and presentation of a NF application (EFSA NDA Panel, 2016). As indicated in this guidance, it is the duty of the applicant to provide all of the available (proprietary, confidential and published) scientific data, (including both data in favour and not in favour) that are pertinent to the safety of the NF.

These NF applications make reference to the proprietary data cited for 2'-FL/DFL mixture (EFSA NDA Panel, 2019a) and for LNT (EFSA NDA Panel, 2019b).

2.2. Methodologies

The assessment follows the methodology set out in the EFSA guidance on NF applications (EFSA NDA Panel, 2016) and the principles described in the relevant existing guidance documents from the EFSA Scientific Committee. The legal provisions for the assessment are laid down in Article 11 of Regulation (EU) 2015/2283 and in Article 7 of the Commission Implementing Regulation (EU) 2017/2469.

This assessment concerns only the risks that might be associated with consumption of the NFs under the proposed conditions of use and is not an assessment of the efficacy of the NFs with regard to any claimed benefit.

3. Assessment

3.1. Introduction

The NFs which are the subject of the application, are human identical milk oligosaccharides (HiMOs) mainly composed of either the 2'-FL/DFL mixture or LNT. As specified in the EU Union list[2] the NFs are produced by fermentation with genetically modified strains of *E. coli* K-12 DH1. They consist, respectively, of ≥ 85% w/w DM 2'-FL/DFL (with 2'-FL ≥ 75% and DFL ≥ 5% w/w DM) or ≥ 70% w/w DM LNT. The remaining fraction of the NFs is composed of other saccharides (e.g. D-lactose).

The NFs are proposed to be used in FS for infants.

According to Regulation (EU) 2015/2283, these NFs fall under the following categories:

i) 'food with a new or intentionally modified molecular structure, where that structure was not used as, or in, a food within the Union before 15 May 1997; and
ii) 'food consisting of, isolated from or produced from microorganisms, fungi or algae'.

3.2. Identity of the NF

The main constituents of the two NFs are, respectively, 2'-FL/DFL and LNT.

The applicant stated that there is no change to the identity of 2'-FL/DFL and LNT as currently approved in the EU Union list.

3.3. Production process

The applicant also stated that the manufacturing conditions for both NFs have not changed.

3.4. History of use of the NF and of its source

3.4.1. History of use of the NF

Both NFs 2'-FL/DFL and LNT mixture are authorised for use in several food categories intended for the general population, including infants. In IF and FOF, the NFs are authorised up to the following maximum use levels:

2'-FL/DFL – In IF, '1.6 g/L in the final product ready for use, marketed as such or reconstituted as instructed by the manufacturer'; in FOF, '1.2 g/L in the final product ready for use, marketed as such or reconstituted as instructed by the manufacturer'.

[3] Commission Implementing Regulation (EU) 2017/2469 of 20 December 2017 laying down administrative and scientific requirements for applications referred to in Article 10 of Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. OJ L 351, 30.12.2017, pp. 64–71.

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LNT – In IF, '0.8 g/L in the final product ready for use, marketed as such or reconstituted as instructed by the manufacturer'; in FOF, '0.6 g/L in the final product ready for use, marketed as such or reconstituted as instructed by the manufacturer'.

3.4.2. Consumption of oligosaccharides constituent of the NFs in human milk

In previous EFSA opinions, the daily intakes of these oligosaccharides from the consumption of human milk have been estimated for a 6.7 kg body weight (bw) infant (EFSA Scientific Committee, 2012), considering the average and high daily intake of human milk (800 mL and 1,200 mL, respectively) for infants from 0 to 6 months (EFSA NDA Panel, 2013).

Specifically, for 2'-FL and DFL, the daily intake ranges from 55 to 856 mg/kg bw, when considering mean and high concentrations in human milk in average and high milk intake scenarios (Table 1).

Table 1: Estimated daily intake levels of 2'-FL and DFL from average (800 mL) and high (1,200 mL) human milk intake for infants of 6.7 kg bw, based on mean and high concentration of 2.38 g/L and 4.78 g/L, respectively, of 2'-FL and mean and high concentration of 0.46 g/L and 2.44 g/L, respectively, of DFL in human milk (Erney et al., 2001; EFSA NDA Panel, 2019a)

	Daily intake levels (mg/kg bw) from 800 mL of human milk		Daily intake levels (mg/kg bw) from 1,200 mL of human milk	
	Mean concentration	High concentration	Mean concentration	High concentration
2'-FL	284	571	426	856
DFL	55	291	82	437

2'-FL: 2'-fucosyllactose; DFL: difucosyllactose; bw: body weight.

For LNT, the daily intake ranges from 91 to 491 mg/kg bw, when considering mean and high concentrations in human milk in average and high milk intake scenarios (Table 2).

Table 2: Estimated daily intake levels of LNT from average (800 mL) and high (1,200 mL) human milk intake for infants of 6.7 kg bw, based on mean and high concentration of 0.76 g/L and 2.74 g/L, respectively, of LNT measured in human milk (Erney et al., 2001; EFSA NDA Panel, 2019b)

	Daily intake levels (mg/kg bw) from 800 mL of human milk		Daily intake levels (mg/kg bw) from 1,200 mL of human milk	
	Mean concentration	High concentration	Mean concentration	High concentration
LNT	91	327	136	491

LNT: lacto-*N*-tetraose; bw: body weight.

3.5. Proposed uses and use levels and anticipated intake

3.5.1. Target population

The target population proposed by the applicant is infants.

3.5.2. Proposed uses and use levels

The applicant intends to market the NFs 2'-FL/DFL mixture and LNT in FS for infants at the proposed maximum use levels given in Table 3.

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Table 3: Maximum proposed use levels of the NFs and their main components

	Age groups	Maximum use level (g/day)	
		NF	HiMO
2′-FL/DFL	Infants ≤ 6 months	1.6	1.30 2′-FL; 0.18 DFL[a]
	Infants > 6 months	1.2	0.97 2′-FL; 0.13 DFL[a]
LNT	Infants ≤ 6 months	1.0[b]	0.8 LNT
	Infants > 6 months	0.8[b]	0.6 LNT

2′-FL: 2′-fucosyllactose; DFL: difucosyllactose; LNT: lacto-*N*-tetraose; NF: novel food; HiMO: human identical milk oligosaccharide.
a: Values estimated considering the average concentration of 2′-FL and DFL (81 and 11% w/w DM, respectively) in the NF (EFSA NDA Panel, 2019a).
b: Values estimated considering the average concentration of LNT (78% w/w DM) in the NF (EFSA NDA Panel, 2019b).

The Panel notes that, according to the specifications, the purity of 2′-FL and DFL in the NF is at least 75% and 5% w/w DM, respectively, with the 2′-FL/DFL mixture accounting for minimum 85% w/w DM of the NF. According to the batch-to-batch analysis, average concentrations of 2′-FL and DFL represent 81% and 11% w/w DM of the NF, respectively (EFSA NDA Panel, 2019a). These values have been used for the estimation of the maximum daily intakes of 2′-FL and DFL from the proposed uses of the NF in FS for infants.

In the specifications of the NF, the concentration of LNT is set as a minimum of 70% w/w DM, with an average purity of 78% w/w DM resulting from the batch-to-batch analysis (EFSA NDA Panel, 2019b). Since the maximum use levels proposed by the applicant (0.6 or 0.8 g/day in FS for infants > 6 months or ≤ 6 months, respectively) are expressed on a LNT basis, the above-mentioned average concentration of LNT in the NF (78% w/w DM), has been used to estimate the corresponding maximum use levels expressed on a NF basis.

The applicant stated that FS containing the NFs are not intended to be used in children under 10 years of age if human milk or foods with added 2′-FL/DFL or LNT are consumed on the same day.

3.5.3. Anticipated intake of the NF

The NFs are proposed to be used in FS for infants.

2′-FL/DFL mixture: According to the maximum proposed use levels of the NF of 1.6 or 1.2 g/day in FS for infants ≤ 6 months or > 6 months, respectively, the estimated daily intakes of the NF and the individual 2′-FL and DFL are reported in Table 4.

Table 4: Maximum daily intake of 2′-FL and DFL from the proposed use of the NF in FS for infants

Population group	Age (months)	Body weight[(a)] (kg)	Use level of the NF (mg/day)	Intake of the NF (mg/kg bw per day)[(b)]	Intake of 2′-FL and DFL (mg/day)[(c)]	Intake of 2′-FL and DFL (mg/kg bw per day)[(b)]
Infants	≤ 6	5.8	1,600	276	1,300 (2′-FL)	224 (2′-FL)
					180 (DFL)	31 (DFL)
	> 6	8.8	1,200	136	970 (2′-FL)	110 (2′-FL)
					130 (DFL)	15 (DFL)

bw: body weight; 2′-FL: 2′-fucosyllactose; DFL: difucosyllactose; NF: novel food.
(a): Default and average body weights for each population group are available in EFSA Scientific committee (2012).
(b): Intake in 'mg/kg bw per day' are calculated by considering the use levels in 'mg/day' and default body weights.
(c): The intake is estimated considering the average composition of the NF: 2′-FL 81% and DFL 11% w/w DM (rounded figures).

The Panel notes that the anticipated maximum daily intakes of 2′-FL and DFL from the proposed uses of the NF in FS for infants are below the lowest estimated mean daily intakes of these oligosaccharides by breastfed infants, expressed on a bw basis (Table 1).

Furthermore, the estimated intake from the proposed use in FS for infants is lower than the estimated intake from the already authorised uses of 2′-FL/DFL in IF (infants of 0-16 weeks) and in other food categories (infants of 4–11 months of age) (EFSA NDA Panel, 2019a).

LNT: According to the maximum proposed use levels of 0.8 or 0.6 g/day LNT in FS for infants ≤ 6 months or > 6 months, respectively, the estimated daily intake of LNT and the NF are reported in Table 5.

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Table 5: Maximum daily intake of LNT from the proposed use in FS for infants

Population group	Age (months)	Body weight[(a)] (kg)	Use level of the NF (mg/day)[(c)]	Intake of the NF (mg/kg bw per day)[(b)]	Intake of LNT (mg/day)	Intake of LNT (mg/kg bw per day)[(b)]
Infants	≤ 6	5.8	1,030	178	800	138
	> 6	8.8	770	88	600	68

LNT: lacto-*N*-tetraose; NF: novel food; bw: body weight.
(a): Default and average body weights for each population group are available in EFSA Scientific committee (2012).
(b): Intakes in 'mg/kg bw per day' are calculated by considering the use levels in 'mg/day' and default body weights.
(c): The intake is estimated considering the average concentration of 78% w/w DM (rounded figures).

The Panel notes that the anticipated maximum daily intake of LNT from the proposed use of the NF in FS for infants is similar to the highest estimated mean daily intake of LNT by breastfed infants, expressed on a bw basis (Table 2).

Furthermore, the estimated intake from the proposed use in FS for infants is lower than the estimated intake from the already authorised uses of LNT in IF (infants of 0–16 weeks) and in other food categories (infants of 4–11 months of age) (EFSA NDA Panel, 2019b).

The applicant stated that FS containing the NFs are not intended to be used in children under 10 years of age if human milk or foods with added 2'-FL/DFL or LNT are consumed on the same day.

3.6. Nutritional information

The NFs are mainly composed of non-digestible oligosaccharides, either 2'-FL/DFL or LNT. The proposed use levels of the NFs in FS for infants are lower than the authorised maximum use levels in FS for the general population: for 2'-FL/DFL, up to 4 g/day of the NF and for LNT, up to 2 g/day. In addition, the intake from the proposed use in FS for infants is lower than the estimated intake from the already authorised uses of the NFs in IF (infants of 0–16 weeks) and in other food categories (infants of 4–11 months of age) (EFSA NDA Panel, 2019a,b).

The Panel considers that the consumption of the NFs at the proposed use levels is not nutritionally disadvantageous.

4. Discussion

The NFs which are the subject of the application, are the already authorised HiMOs 2'-FL/DFL mixture and LNT. As specified in the Union list,[1] the NFs are produced by fermentation with genetically modified strains of *E. coli* K-12 DH1 and consist of ≥ 70% w/w DM LNT or ≥ 75% and ≥ 5% w/w DM 2'-FL and DFL (minimum of 85% as mixture), respectively. The remaining fraction of the NFs is composed of other saccharides (e.g. D-lactose).

The NF containing 2'-FL/DFL is proposed to be used at the maximum use levels of 1.6 or 1.2 g/day in FS for infants ≤ 6 months or > 6 months, respectively. Likewise, LNT is proposed to be used at 0.8 or 0.6 g/day in FS for infants ≤ 6 months or > 6 months, respectively.

The Panel notes that the maximum daily intakes of 2'-FL/DFL and LNT in FS for infants are lower than the estimated intake from the already authorised uses in IF (infants of 0–16 weeks) and in other food categories (infants of 4–11 months of age) (EFSA NDA Panel, 2019a,b).

Moreover, the maximum daily intakes of the NFs from the proposed use levels in FS for infants are below or similar to the estimated mean daily intakes of 2'-FL/DFL or LNT by breastfed infants, expressed on a bw basis.

5. Conclusions

The Panel concludes that the uses of the NFs containing either 2'-FL/DFL or LNT, in FS for infants are safe under the proposed conditions of use.

FS containing the NFs are not intended to be used if human milk or foods with added 2'-FL/DFL and LNT are consumed on the same day.

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6. Steps taken by EFSA

1) On 16/06/2021 EFSA received a letter from the European Commission with the request for a scientific opinion on the safety of the extension of the use of the authorised NFs 2'-FL/DFL mixture and LNT in FS for infants (Ref. Ares(2021)3938205).
2) On 16/06/2021, a valid application on 2'-FL/DFL mixture and LNT for use in FS for infants, which was submitted by Glycom A/S, was made available to EFSA by the European Commission through the Commission e-submission portal (NF 2021/0090 and NF 2021/0091) and the scientific evaluation procedure was initiated.
3) During its meeting on 26/01/2022, the NDA Panel, having evaluated the data, adopted a scientific opinion on the safety of the extension of use of the authorized NFs 2'-FL/DFL mixture and LNT in FS for infants pursuant to Article 10 of Regulation (EU) 2015/2283 Novel food.

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Abbreviations

2'-FL	2'-fucosyllactose
bw	body weight
DFL	difucosyllactose
DM	dry matter
FOF	follow-on formulae
FS	food supplement
HiMO	Human identical milk oligosaccharides
IF	infant formulae
LNT	lacto-*N*-tetraose
NDA Panel	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NF	novel food
w/w	weight for weight

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