SCIENTIFIC OPINION

efsa JOURNAL

ADOPTED: 26 September 2023

doi: 10.2903/j.efsa.2023.8334

Safety of the extension of use of 2′-fucosyllactose (2′-FL) as a novel food pursuant to Regulation (EU) 2015/2283

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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 extension of use of 2′-fucosyllactose (2′-FL) as a novel food (NF) pursuant to Regulation (EU) 2015/2283. The NF is already authorised as ingredient in several food categories, including infant formula (IF) and follow-on formula (FOF). The applicant proposed to increase the maximum use levels of the NF in IF and FOF. EFSA estimated the anticipated daily intake of the NF from the proposed extension of use, including the already authorised conditions of use in other food categories. Additionally, a new intake estimate limited to the already authorised conditions of use of the NF was carried out following EFSA's current approach. The estimated daily intake of the NF from high consumption of IF alone at the proposed maximum use level in infants < 16 weeks of age is similar to the estimated natural highest mean daily intake of 2′-FL from human milk in breastfed infants. The estimated highest P95 daily intakes of the NF from the proposed extension of use in IF and FOF (including the authorised uses in other food categories) and from the already authorised conditions of use, are comparable and both higher than the estimated natural highest mean daily intake of 2′-FL from human milk in infants and to a lesser extent in young children. The Panel considers that the proposed extension of use of the NF in IF and FOF only marginally affects the highest P95 daily intake estimate from the authorised conditions of use, and therefore does not affect the safety of the NF. The Panel concludes that the NF, 2′-FL, is safe under the proposed conditions of use.

Keywords: 2′-FL, 2′-fucosyllactose, HiMO, novel foods, extension of use, infant formula, infants

Requestor: European Commission

Question number: EFSA-Q-2021-00643

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Declarations of interest: If you wish to access the declaration of interests of any expert contributing to an EFSA scientific assessment, please contact interestmanagement@efsa.europa.eu.

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, K. I., Maciuk, A., Mangelsdorf, I., McArdle, H. J., Naska, A., Pentieva, K., Siani, A., Thies, F., Tsabouri, S., Vinceti, M., Aguilera-Gómez, M., Cubadda, F., Frenzel, T., Heinonen, M., … Knutsen, H. K. (2023). Safety of the extension of use of 2′-fucosyllactose (2′-FL) as a novel food pursuant to Regulation (EU) 2015/2283. *EFSA Journal*, *21*(11), 1–13. https://doi.org/10.2903/j.efsa.2023.8334

ISSN: 1831-4732

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 30 June 2021, the company Chr. Hansen 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 novel food (NF) 2′-fucosyllactose (2′-FL).

The application originally requests to authorise an increase in the maximum use levels of 2′-FL in a number of foods intended for infants and young children. During the course of the assessment the applicant modified the request that is currently focused exclusively on infant formula (IF) and follow-on formula (FOF).

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 proposed extension of use of the NF 2′-FL.

1.2. Additional information

2′-FL is included in the Union list of authorised NFs (Commission Implementing Regulation (EU) 2017/2470 of 20 December 2017[2]) when chemically synthesised (Commission Implementing Decision (EU) 2016/376[3]) (EFSA NDA Panel, 2015) or produced by fermentation by genetically modified strains of *Escherichia coli* K-12 DH1 (Commission Implementing Regulation (EU) 2019/338[4]), *E. coli* BL21 (DE3)(Commission Implementing Regulation (EU) 2017/2201[5]) or *Corynebacterium glutamicum* ATCC 13032 (Commission Implementing Regulation (EU) 2023/859[6]) (EFSA NDA Panel, 2022c). Moreover, a 2′-FL/difucosyllactose (DFL) mixture produced by a genetically modified strain of *E. coli* K-12 DH1 is also included in the Union list of authorised NFs (EFSA NDA Panel, 2019a). The extension of use in food supplements (FS) for infants of 2′-FL and lacto-N-neotetraose (LNnT) produced by genetically modified strains of *E. coli* K-12 DH1 or 2′-FL/DFL and lacto-N-tetraose (LNT) produced by genetically modified strains of *E. coli* K-12 DH1 has also been assessed by EFSA with positive outcomes (EFSA NDA Panel, 2022b,c).

2. Data and methodologies

2.1. Data

The safety assessment of this NF is based on data supplied in the application and information submitted by the applicant following EFSA's requests for supplementary information.

Administrative and scientific requirements for NF applications referred to in Article 10 of Regulation (EU) 2015/2283 are listed in Commission Implementing Regulation (EU) 2017/2469[7].

[1] Regulation (EU) 2015/2283 of the European Parliament and of the council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001; 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 in accordance with Regulation (EU) 2015/2283 of the European Parliament and of the Council on novel foods. OJ L 351, 30.12.2017, pp. 72–201.

[3] Commission Implementing Decision (EU) 2016/376 of 11 March 2016 authorising the placing on the market of 2′-O-fucosyllactose as a novel food ingredient under Regulation (EC) No 258/97 of the European Parliament and of the Council. OJ L 70, 16.3.2016, pp. 27–31.

[4] Commission Implementing regulation (EU) 2019/338 of 11 March 2019 authorising the change of the specifications of the novel food 2′-fucosyllactose produced with *Escherichia coli* K-12 under Regulation (EU) No 2015/2283 of the European Parliament and of the Council. OJ L 70, 12.3.2019, pp. 21–24.

[5] Commission Implementing regulation (EU) 2017/2201 of 27 November 2017 authorising the placing on the market of 2′-fucosyllactose produced with *Escherichia coli* strain BL21 as a novel food ingredient under Regulation (EC) No 258/97 of the European Parliament and of the Council. OJ L 313, 29.11.2017, pp. 5–9.

[6] Commission Implementing Regulation (EU) 2023/859 of 25 April 2023 amending Implementing Regulation (EU) 2017/2470 as regards the specifications of the novel food 2′-Fucosyllactose (microbial source) to authorise its production by a derivative strain of *Corynebacterium glutamicum* ATCC 13032; OJ L 111, 25.4.2023, pp.17–22.

[7] 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.

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, 2021). 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.

The applicant has submitted a confidential and a non-confidential version of a dossier following the EFSA guidance on the preparation and presentation of a NF application (EFSA NDA Panel, 2021) and the 'Administrative guidance for the preparation of applications on novel foods pursuant to Article 10 of Regulation (EU) 2015/2283' (EFSA, 2021).

In accordance with Art. 38 of Regulation (EC) No 178/2002[8] and taking into account the protection of confidential information and of personal data in accordance with Articles 39 to 39e of the same Regulation, and of the Decision of EFSA's Executive Director laying down practical arrangements concerning transparency and confidentiality,[9] the non-confidential version of the dossier has been published on Open.EFSA.[10]

According to Art. 32c(2) of Regulation (EC) No 178/2002 and to the Decision of EFSA's Executive Director laying down the practical arrangements on pre-submission phase and public consultations,[9] EFSA carried out a public consultation on the non-confidential version of the technical dossier from 5 April to 26 April 2023 for which no comments were received.

2.2. Methodologies

The assessment follows the methodology set out in the EFSA Guidance on NF applications (EFSA NDA Panel, 2021) and the principles described in the relevant existing guidance documents from the EFSA Scientific Committee.

The legal provisions for the assessment of novel foods are laid down in Article 11 of Regulation (EU) 2015/2283 and in Article 7 of Commission Implementing Regulation (EU) 2017/2469. The legal provisions for the assessment of food intended for infants and young children, are laid down in Regulation (EU) 609/2013 and in Commission Delegated Regulation (EU) 2016/127 (as regards the specific compositional and information requirements for IF and FOF and as regards requirements on information relating to infant and young child feeding).

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

3. Assessment

3.1. Introduction

The NF which is the subject of the application is 2′-FL, a human-identical milk oligosaccharide (HiMO). The NF is already authorised (Regulation (EU) 2017/2470[2]) and no changes in the production process were introduced as per the previous safety assessment (Regulation (EU) 2017/2201[5]). The applicant requests an extension of use of the NF by proposing an increase in the maximum use levels of the NF as an ingredient in IF and FOF. The target population for the proposed extension of use is infants and young children.

According to Regulation (EU) 2015/2283, the NF falls 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'.

[8] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety. OJ L 31, 1.2.2002, pp.1–48.

[9] Decision available at: https://www.efsa.europa.eu/en/corporate-pubs/transparency-regulation-practical-arrangements.

[10] The non-confidential version of the dossier has been published on Open.EFSA and is available at the following link: https://open.efsa.europa.eu/dossier/NF-2021-1171.

3.2. Identity of the NF

The NF is 2′-FL produced by a genetically modified strain of *E. coli* BL21 (DE3).

The applicant stated that there is no change to the identity of 2′-FL as currently approved in the Union list.[2]

3.3. Production process

The applicant stated that the manufacturing conditions for the NF have not changed.

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

3.4.1. History of use of the NF

The NF is authorised as an ingredient in IF and FOF, and in several other food categories intended for the general population, including infants.

Specifically, in IF and FOF the NF is authorised up to '1.2 gram of 2′-FL per litre final product ready for use marketed as such or reconstituted as instructed by the manufacturer'[2].

3.4.2. Intake of 2′-FL from human milk

In previous EFSA opinions (EFSA NDA Panel, 2022a,b), the daily intake of 2′-FL from the consumption of human milk was estimated for a 6.7-kg body weight (bw) infant (EFSA Scientific Committee, 2012), considering the average and high daily intakes of human milk (800 and 1,200 mL, respectively) for infants from 0 to 6 months (EFSA NDA Panel, 2013). Average (2.38 g/L) and maximum (4.78 g/L) concentrations of 2′-FL in human milk reported by Erney et al. (2001) were used in intake estimations (EFSA NDA Panel, 2019a, 2022a,b). More recently, in consideration of the large and recent data set used in the review by Soyyılmaz et al. (2021), the Panel has decided to use the values reported there for the intake assessments of HiMOs (e.g. EFSA NDA Panel, 2022d–f, 2023). For 2′-FL, those values correspond to the mean of mean concentrations (2.28 g/L) and the maximum mean (4.28 g/L) concentration across studies (Soyyılmaz et al., 2021) and are considered as representative of the concentration range found in mature human milk. The estimated natural intakes of 2′-FL based on Soyyılmaz et al. (2021) are reported in Table 1. The Panel also notes that due to the relatively wide concentration range of 2′-FL in human milk (up to 4.78 g/L – Thurl et al., 2017; 5.57 g/L – Austin et al., 2019; 5.85 g/L Samuel et al., 2019), higher natural intakes of 2′-FL may occur.

Table 1: Estimated daily intakes of 2′-FL from average (800 mL) and high (1,200 mL) daily intakes of human milk for infants of 6.7 kg bw, based on the mean of mean concentrations (2.28 g/L) and the maximum mean (4.28 g/L) concentration of 2′-FL in mature human milk (lactation days 15–90; Soyyılmaz et al., 2021)

	Daily intake of 2′-FL (mg/kg bw) from 800 mL/day of human milk		**Daily intake of 2′-FL (mg/kg bw) from 1,200 mL/day of human milk**	
	Mean of mean concentrations	**Maximum mean concentration**	**Mean of mean concentrations**	**Maximum mean concentration**
2′-FL	272	511	408	767

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 for this extension of use is infants and young children.

3.5.2. Proposed uses and use levels

The applicant proposes an increase in the authorised maximum levels of the NF in IF and FOF, from the authorised 1.2 g/L (in both) to 3.0 g/L in IF and 3.64 g/L in FOF.

No changes to the already authorised use levels for the remaining food categories (Appendix A) are proposed.

3.5.3. Anticipated intake of the NF

Anticipated intake of the NF from the consumption of IF in infants up to 16 weeks of age

IF is expected to be the only food consumed by infants aged 0–16 weeks who are not breastfed. A high consumption of IF has been estimated to be 260 mL/kg bw per day for infants aged 0–16 weeks (EFSA Scientific Committee, 2017). Based on the proposed maximum use level of the NF in IF (3.0 g/L), the high intake of the NF from IF alone is estimated to be 780 mg/kg bw per day.

The Panel notes that the anticipated daily intake of the NF from high consumption of IF alone at the proposed maximum use level is similar to the estimated natural highest mean daily intake of 2′-FL from human milk of 767 mg/kg bw (see Table 1).

Anticipated intake of the NF from the proposed uses and use levels

EFSA estimated the anticipated daily intake of the NF from the proposed extension of use in IF and FOF (3.0 g/L for IF and 3.64 g/L for FOF), also including the already authorised conditions of use of the NF as ingredient in other food categories (see Appendix A) and using the EFSA Dietary Exposure (DietEx) tool,[11] which is based on individual data from the EFSA Comprehensive European Food Consumption Database (EFSA, 2011). The lowest and highest mean and 95th percentile anticipated daily intakes of the NF (on a mg/kg bw basis), among the EU dietary surveys, are presented in Table 2.

The estimated daily intake of the NF for each population group from each EU dietary survey is available in the excel file annexed to this scientific opinion (under supporting information).

Table 2: Intake estimate of the NF from the proposed extension of use in IF and FOF and the already authorised conditions of use

Population group	Age (years)	Mean intake (mg/kg bw per day)		P95 intake (mg/kg bw per day)	
		Lowest[(a)]	Highest[(a)]	Lowest[(b)]	Highest[(b)]
Infants	< 1	113	568	291	1,382
Young children[(c)]	1 to < 3	123	439	340	881
Other children	3 to < 10	45	198	141	605
Adolescents	10 to < 18	14	81	52	233
Adults[(d)]	≥ 18	37	153	100	337

bw: body weight.
(a): Intakes are assessed for all EU dietary surveys available in the food comprehensive database on 5 July 2023. The lowest and the highest averages observed among all EU surveys are reported in these columns.
(b): Intakes are assessed for all EU dietary surveys available in the food comprehensive database on 5 July 2023. The lowest and the highest P95 observed among all EU surveys are reported in these columns (P95 based on less than 60 individuals are not considered).
(c): Referred as 'toddlers' in the EFSA food consumption comprehensive database (EFSA, 2011).
(d): Includes elderly, very elderly, pregnant and lactating women.

The proposed extension of use only concerns IF and FOF. Considering that the previous estimate of the NF intake from the authorised conditions of use was based on a different approach and databases (2008–2010 UK data) (EFSA NDA Panel, 2015) to what is currently used by EFSA, the intake of the NF from the already authorised conditions of use (including 1.2 g/L for IF and FOF) was also estimated using the DietEx tool (Table 3) and annexed to this scientific opinion (under supporting information).

[11] https://www.efsa.europa.eu/it/science/tools-and-resources/dietex.

Table 3: Intake estimate of the NF from the already authorised conditions of use

Population group	Age (years)	Mean intake (mg/kg bw per day)		P95th intake (mg/kg bw per day)	
		Lowest[(a)]	Highest[(a)]	Lowest[(b)]	Highest[(b)]
Infants	< 1	51	438	132	1,377
Young children[(c)]	1 to < 3	116	398	292	869
Other children	3 to < 10	45	198	140	605
Adolescents	10 to < 18	14	81	52	233
Adults[(d)]	≥ 18	36	153	95	337

bw: body weight.
(a): Intakes are assessed for all EU dietary surveys available in the food comprehensive database on 5 July 2023. The lowest and the highest averages observed among all EU surveys are reported in these columns.
(b): Intakes are assessed for all EU dietary surveys available in the food comprehensive database on 5 July 2023. The lowest and the highest P95 observed among all EU surveys are reported in these columns (P95 based on less than 60 individuals are not considered).
(c): Referred as 'toddlers' in the EFSA food consumption comprehensive database (EFSA, 2011).
(d): Includes elderly, very elderly, pregnant and lactating women.

The Panel notes that in infants and to a lesser extent in young children, the highest P95 daily intake of the NF from the proposed extension of use in IF and FOF (including the authorised conditions of use in other food categories) (Table 2) is higher than the estimated natural highest mean daily intake in breastfed infants (767 mg/kg bw – Table 1). According to EFSA's current intake assessment approach using the DietEx tool, the highest P95 daily intake of the NF from the already authorised conditions of use as an ingredient (Table 3) is also higher than the estimated natural highest mean daily intake, although very similar to the highest P95 daily intake from the proposed extension of use. The NDA Panel notes that the applicant's proposed increase in use levels in IF and FOF only marginally affects the highest 95th percentile intakes of 2′-FL in infants and young children.

3.6. Nutritional information

The NF consists of a non-digestible oligosaccharide, 2′-FL. The highest P95 daily intake of the NF from the proposed extension of use in IF and FOF (including the authorised conditions of use in other food categories) is similar to that from the already authorised conditions of use of the NF as an ingredient.

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

3.7. Human data

No human intervention studies conducted with 2′-FL alone have been provided by the applicant.

However, the applicant made reference to a multicentre, randomised, controlled, parallel-group clinical study conducted in infants (Parschat et al., 2021) with IF containing a mixture of HiMOs (composed by 2′-FL (52.0%), 3-fucosyllactose (13.0%), LNT (26.0%), 3′-sialyllactose sodium salt (4.0%), 6′-sialyllactose sodium salt (5.0%)) at a concentration of 5.75 g/L, corresponding to 2.99 g/L of 2′-FL. The main goal of the study was to investigate the suitability of the HiMO mixture in IF to support normal physical growth (evaluated in terms of weight gain), in comparison with standard IF and breastfed infants. The multicentre study comprised three parallel arms consisting of two randomised, double-blinded intervention groups receiving either IF or IF supplemented with the HiMO mixture and a third group of breastfed infants as a reference group. The study was conducted over a 16-week period in a total of 341 subjects. Secondary endpoints of tolerability (e.g. stool frequency and consistency, digestive tolerance) were also assessed. The safety and tolerability profile of the HiMO mixture in IF appeared to be similar to that of the commercialised IF alone. The authors concluded that the HiMO mixture at 5.75 g/L (2.99 g/L of 2′-FL) in IF is safe and well tolerated by healthy term infants during the first months of life.

The Panel considers the information provided by the applicant as supportive for the assessment of 2′-FL.

4. Discussion

The NF which is the subject of the application is the already authorised HiMO 2′-FL. As specified in the Union list,[2] the NF is produced by fermentation by a genetically modified strain of *E. coli* BL21 (DE3).

An increase in the maximum use levels of the NF in IF (3.0 g/L) and FOF (3.64 g/L) from the authorised 1.2 g/L (for both) is proposed, while no changes in other authorised conditions of use of the NF are intended.

IF is intended for use 'by infants during the first months of life and satisfying by itself the nutritional requirements of such infants until the introduction of appropriate complementary feeding' (Reg. (EU) No 609/2013[12]). Complementary foods are then necessary to meet infant's need for energy and nutrients from the age of 4–6 months (WHO, 2001, 2006; EFSA NDA Panel, 2019b). The Panel notes that the anticipated daily intake of the NF from high consumption of IF alone at the proposed maximum use level in infants up to 16 weeks of age (780 mg/kg bw) is similar to the estimated natural highest mean daily intake of 2′-FL from human milk (767 mg/kg bw).

The Panel notes that in updated exposure estimates the already authorised use of 2′-FL results in intakes that are higher than the estimated natural highest mean daily intake in breastfed infants when compared on a per kg bw basis. However, the Panel also notes that the applicant's suggested increase in use levels in IF and FOF only marginally affects the highest P95 intakes of 2′-FL in infants and young children.

The Panel considers that the proposed increase of use levels of the NF in IF and FOF only marginally affects the highest P95 daily intake estimate from the authorised conditions of use of the NF as an ingredient, and therefore does not affect the safety of the NF.

5. Conclusions

The Panel concludes that the NF, 2′-FL, is safe under the proposed conditions of use.

6. Steps taken by EFSA

1) On 28 September 2022 EFSA received a letter from the European Commission with the request for a scientific opinion on the safety of the extension of use of 2′-FL Ref.Ares(2022) 6681508.
2) On 28 September 2022, a valid application on the extension of use of 2′-FL, which was submitted by Chr. Hansen A/S, was made available to EFSA by the European Commission through the Commission e-submission portal (NF 2021/1171) and the scientific evaluation procedure was initiated.
3) On 20 December 2022 and 28 February 2023, EFSA requested the applicant to provide additional information to accompany the application and the scientific evaluation was suspended.
4) On 07 February 2023 and 29 March 2023, additional information was provided by the applicant through the Commission e-submission portal and the scientific evaluation was restarted.
5) During its meeting on 26 September 2023, the NDA Panel, having evaluated the data, adopted a scientific opinion on the safety of the extension of use of 2′-FL as a NF pursuant to Regulation (EU) 2015/2283.

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Abbreviations

2′-FL	2′-Fucosyllactose
ATCC	American Type Culture Collection
bw	body weight
DFL	difucosyllactose
DietEx	EFSA Dietary Exposure tool
FOF	follow-on formula
FS	food supplements
HiMO	human-identical milk oligosaccharide
HMO	human milk oligosaccharide
IF	infant formula
LNnT	lacto-N-neotetraose
LNT	lacto-N-tetraose
NDA	EFSA Panel on Nutrition, Novel Foods and Food Allergens
NF	novel food
WHO	World Health Organization

Appendix A – Food categories and maximum use levels intended by the applicant

FoodEx2 level	FoodEx2 code	Food category	Max proposed use level	Authorised use level
			(mg NF/100 g)	
1	A03GG	Coffee, cocoa, tea and infusions	960	
2	A03RC	Ready-to-eat meal for infants and young children	1,200	
2	A0F7R	Table-top sweeteners formulations	20,000	
3	A00EY	Cereal bars	1,200	
3	A02MV	Buttermilk	120	
3	A03QY	Simple cereals which have to be reconstituted with milk or other appropriate nutritious liquids	840	
3	A03QZ	Cereals with an added high-protein food which have to be reconstituted with water or other protein-free liquid	480	
3	A03RA	Biscuits, rusks and cookies for children	1,200	
3	A03RB	Pasta for children (dry, to be cooked)	1,200	
3	A03RN	Fruit and vegetable juices and nectars specific for infants and young children	120	
3	A03RP	Special food for children's growth	120	
3	A0BZE	Simple cereals for infants or children, reconstituted	120	
3	A0BZF	Cereals with an added high-protein food reconstituted	120	
4	A005R	Gluten free bread	6,000	
4	A02MB	Goat milk	120	
4	A02NE	Yoghurt	1,920	
4	A02NQ	Yoghurt drinks, including sweetened and/or flavoured variants	120	
4	A02NR	Probiotic milk-like drinks	120	
4	A03FQ	Cola-type drinks	120	
4	A03PZ	Infant formulae, powder	2,400	960
4	A03QE	Infant formulae, liquid	300	120
4	A03QK	Follow-on formulae, powder	2,912	960
4	A03QQ	Follow-on formulae, liquid	364	120
4	A03RT	Total daily diet replacement for weight reduction	4,000	
4	A03TH	Milk imitates	120	
4	A03TQ	Dairy imitates other than milks	40,000	
4	A0EQN	Soft drinks with minor amounts of fruits or flavours	120	
5	A008B	Pasta, gluten free	6,000	
5	A02LV	Cow milk	120	
5	A02MC	Sheep milk	120	
5	A02NV	Kefir	120	
5	A0CXA	European buffalo milk	120	

Newly proposed use levels highlighted, remaining ones already authorised.

Annex A – Dietary exposure estimates to the Novel Food for each population group from each EU dietary survey (proposed and authorised uses and use levels)

Information provided in this Annex can be found in the online version of this output (in the Supporting information' section).