REGULATED PRODUCTS SAFETY ASSESSMENT

Assessment of Novel Food 2'-Fucosyllactose (2'-FL) for a Change to the Conditions of Use as a Food Ingredient (RP2155)

Food Standards Agency[1], Food Standards Scotland[2]

[1] Regulated Products Risk Assessment, Food Standards Agency, UK, [2] Risk Assessment , Food Standards Scotland, UK

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FSA Research and Evidence

Chr. Hansen, Denmark ("the applicant") submitted a novel food application for a change to intended conditions of use of 2'-fucosyllactose as a novel food ingredient to each nation of Great Britain in December 2023.

2'-Fucosyllactose (2'-FL) has been the subject of several prior applications in the EU, under the previous novel food Regulation (EC) 258/97 and assimilated Regulation (EU) 2015/2283 applicable to GB. 2'-FL manufactured by microbial fermentation using a genetically modified strain of *Escherichia coli* BL21 was authorised in the EU (and UK) in 2017 following an opinion through the 'initial assessment' process of Regulation (EC) 258/97 by the Medicines Evaluation Board of the Netherlands (MEB) (MEB, 2016). 2'-FL is currently authorised for use in several food and drinks categories for the general population and for infants and young children, including infant formula (IF) and follow-on formula (FoF) at a level of 1.2 g/L.

In accordance with assimilated Regulation (EU) 2015/2283 on novel foods, the application RP2155 to change the conditions of use of 2'-fucosyllactose (2'-FL) as a novel food, has been submitted for authorisation in each nation of Great Britain (GB). This application seeks to modify the conditions of use in IF and FoF at maximum intake levels higher than currently authorised levels. 2'-FL is a human-identical milk oligosaccharide (HiMO).

This change to the conditions of use of the 2'-FL novel food ingredient had its application for authorisation assessed by the European Food Safety Authority (EFSA), which was published in September 2023. The Food Standards Agency (FSA) and Food Standards Scotland (FSS) have reviewed the information available, including the EFSA opinion, and confirmed that 2'-FL is safe under the proposed change to the conditions of use. The anticipated intake levels were not considered to be nutritionally disadvantageous.

This is a joint FSA and FSS publication.

1. Introduction

2'-Fucosyllactose is an authorised novel food in the UK (assimilated Commission Implementing Regulation (EU) 2017/2470). In accordance with assimilated Regulation (EU) 2015/2283 on novel foods, the application RP2155 was submitted for a change in the conditions of use of 2'-fucosyllactose to increase the use level in infant formula (IF) and follow-on formula (FoF) in each nation of Great Britain (GB).

Whilst it was a Member State of the EU, the UK accepted the risk assessments of the European Food Safety Authority (EFSA) in respect of authorisations for regulated food and feed products. Since the end of the transition period, the FSA and FSS have adopted equivalent technical guidance and quality assurance processes to be able to undertake GB risk assessments for regulated product applications.

To ensure our regulatory systems are risk proportionate and resources are used effectively, the FSA and FSS have used the evidence submitted by the applicant and other information in the public domain, including the EFSA risk assessment opinion, to inform this assessment.

The FSA and FSS have evaluated the published EFSA risk assessment on the novel food and confirmed that this is appropriate for GB risk analysis. Consideration has been given to the processes undertaken to ensure the EFSA opinion is robust, and whether there are any aspects that would require further review, such as specific issues for the countries of GB. The result of the assessment is that there is sufficient evidence of safety to conclude without requiring further risk assessment at this time.

This assessment represents the opinion of the FSA and FSS.

2. Details of other regulators opinions

The applicant, Chr. Hansen A/S (Denmark), is seeking authorisation of a change to the conditions of use of the novel food 2'-fucosyllactose produced by fermentation by a genetically modified strain of *Escherichia coli* BL21 (DE3), to increase the permitted use levels in IF and FoF.

2'-FL is not a new novel food ingredient and under Regulation (EC) 258/97 and assimilated Regulation (EU) 2015/2283, 2'-FL has been the subject of several novel food applications in the EU and applicable to GB.

Use of 2'-FL chemically synthesised or produced by fermentation by genetically modified strains of *E. coli* K-12 (DH1) or *E. coli* BL21 (DE3) are currently authorised novel foods in GB under assimilated Commission Implementing Regulation (EU) 2017/2470 (EFSA NDA Panel, 2015a; assimilated Commission Implementing Decision (EU) 2016/376; assimilated Commission Implementing Regulation (EU) 2019/388; assimilated Commission Implementing Decision (EU) 2017/2201 respectively). Use of 2'-FL in mixture with difucosyllactose (DFL), produced by a genetically modified strain of *E. coli* K-12 (DH1), is also authorised in GB under assimilated Commission Implementing Regulations (EU) 2019/1979 (EFSA NDA Panel, 2019).

2'-FL is authorised for use in IF and FoF, as well as several food and drinks categories for the general population.

Extensions of use of 2'-FL produced by genetically modified strains of *E. coli* K-12 (DH1), alone or in mixture with lacto-N-neotetraose (LNnT) or lacto-N-tetraose (LNT), to food supplements for infants were reviewed by EFSA and received positive opinions (EFSA NDA Panel, 2022a, 2022b).

2'-FL produced by fermentation using genetically modified *E. coli* BL21 (DE3) is also permitted to use in IF, FoF, and other products in the USA (through the Generally Regarded as Safe (GRAS) scheme, FDA, 2015; FDA 2021; FDA 2022), and in Australia and New Zealand (FSANZ, 2021). In addition, its use as an ingredient in IF did not raise any concern in Canada (Health Canada, 2018).

In September 2023, the safety of a change in the conditions of use of 2'-fucosyllactose produced by fermentation using genetically modified *E. coli* BL21 (DE3) (Chr. Hansen A/S, Denmark), for its use as a novel food ingredient in IF and FoF at a higher use level, was assessed by EFSA and received a positive opinion (EFSA NDA Panel, 2023; Commission Implementing Regulation (EU) 2024/2102). This opinion has been reviewed by FSA and FSS risk assessors to inform the view on this application received by countries in GB.

2.1. Methodology applied in the EFSA opinion

The EFSA assessment was conducted in accordance with the procedure as outlined in the EFSA scientific opinion 'Guidance on the preparation and presentation of an application for authorisation of a novel food' in the context of assimilated Regulation (EU) 2015/2283 (EFSA, 2021) and assimilated Commission Implementing Regulation (EU) 2017/2469.

Under Article 3(4) of assimilated Commission Implementing Regulation (EU) 2017/2469, it may not be necessary for the applicant to provide all the data required under Article 5 of this Regulation when a novel food application seeks to modify the conditions of use, the specifications, additional specific labelling requirements or post-market monitoring requirements of an authorised novel food. Verifiable justification explaining that the proposed changes do not affect the results of the existing assessment is provided by the applicant. Given that the novel food is identical to the one reviewed in the previous assessment, this new assessment has focused on the impact of the proposed changes of use for 2'-FL.

The novel food was already assessed and authorised under assimilated Commission Implementing Decision (EU) 2017/2201. This resulted in the inclusion of 2'-FL produced with a genetically modified strain of *E. coli* BL21 on the permitted list of novel foods in the EU and UK (assimilated Commission Implementing Regulation (EU) 2017/2470). As the identity of the novel food and its production process remain unchanged, the conclusions drawn from the information provided in the original application on the identity of the novel food, production process, compositional information, stability, specification, absorption, distribution, metabolism and excretion (ADME) and allergenicity, would not be affected by the proposed change in conditions of use. Therefore, this information was not provided or reviewed as part of the assessment.

The FSA and FSS agree with the view that the changes in the conditions of use do not alter the previous assessment of the novel food composition and specification or the conclusion that no safety concerns have been identified. As such, the focus of this review has been the impact of the changes to the conditions of use: increased levels of 2'-FL in IF and FoF.

2.1.1. Identity of the novel food

The novel food is 2′-fucosyllactose (2'-FL) produced with a genetically modified strain of *E. coli* BL21 (DE3).

The identity of the novel food is not changed by the current application made to the FSA and FSS and as such has not been subject to further assessment. The characterisation of the novel food ingredient below is provided as per the existing authorisation and as assessed by EFSA.

2.1.2. Production process

The applicant stated that the production process of the novel food 2'-FL in the current application is identical to the production process of the 2'-FL produced by microbial fermentation by a genetically modified strain of *E. coli* BL21 (DE3) as authorised in assimilated Commission Implementing Decision (EU) 2017/2201.

The unchanged production process has not been subject to further assessment.

2.1.3. Compositional information and specification

The applicant stated that the composition for 2'-FL produced with a genetically modified strain of *E. coli* BL21 (DE3) is unchanged from the composition as assessed and authorised in assimilated Commission Implementing Decision (EU) 2017/2201. The applicant confirmed that the final product is free of the production organism and of any recombinant genetic material, and mainly consists of the substance 2'-FL and minor portions of other carbohydrate byproducts.

Further review of the compositional analysis was not considered necessary by the FSA and FSS.

The specification for the novel food (Table 1) is currently defined in the List of Novel Foods (assimilated Commission Implementing Regulation (EU) 2017/2470).

Table 1. Specification for the novel food reproduced from the List of Novel Foods (assimilated Commission Implementing Regulation (EU) 2017/2470)

Parameter	Specification
2'-fucosyllactose	≥ 90% DM
Lactose	≤ 5% DM
3-fucosyllactose	≤ 5% DM
Difucosyllactose	≤ 5% DM
Fucosylgalactose	≤ 3% DM
Glucose	≤ 3% DM
Galactose	≤ 3% DM
Fucose	≤ 3% DM
Water	≤ 9 %
Ash	≤ 0.5 %
Protein content	≤ 100 µg/g
Arsenic	≤ 0.2 mg/kg
Lead	≤ 0.02 mg/kg
Cadmium	≤ 0.1 mg/kg
Mercury	≤ 0.5 mg/kg
Aflatoxin M1	≤ 0.025 µg/kg

Parameter	Specification
Standard plate count	≤ 10,000 CFU/g
Yeast and mould	≤ 100 CFU/g
Enterobacteriaceae/coliforms	Absent in 11g
Salmonella spp.	Absent in 100g
Cronobacter spp.	Absent in 100g
Endotoxins	≤ 10 EU/mg

DM = Dry matter; CFU = Colony forming unit; EU/mg = endotoxin unit per milligram

2.1.4. History of use

2'-FL is one of the most predominant human milk oligosaccharides in human milk. The concentration of 2'-FL varies with the secretor profile of lactating women, and with time during lactation (Lagström et al., 2020; Lefebvre et al., 2020; Samuel et al., 2019). A recent review of published studies reporting a mean of mean concentration of 2.28 g/L and a maximum mean concentration of 4.28 g/L (Soyyılmaz et al., 2021) was referenced by EFSA.

Using these values and considering the average and high daily intake of breast milk (800 mL and 1,200 mL, respectively) for infants from 0 to 6 months (EFSA NDA Panel, 2013), the 95th percentile daily anticipated intake levels of 2'-FL from human milk for a 6.7 kg body weight (BW) infant are 511 mg/kg BW/day (800 ml) and 767 mg/kg BW/day (1,200 ml).

EFSA noted that higher intakes may occur, as even higher concentrations of 2'-FL have been reported in human milk (up to 4.78 g/L (Thurl et al., 2017); 5.57 g/L (Austin et al., 2019); and 5.85 g/L (Samuel et al., 2019)).

2'-FL produced by fermentation using genetically modified *E. coli* BL21 (DE3) (Chr. Hansen A/S, Denmark) is already authorised as a novel food in GB (assimilated Commission Implementing Regulation (EU) 2017/2470) for use in several categories of foods and beverages, including foods for special groups, and supplements. As per this Regulation, 2'-FL is already authorised in IF and in FoF at maximum use levels of 1.2 g/L in the final product ready for use, marketed as such or reconstituted as instructed by the manufacturer.

2'-FL obtained by the same production process is also authorised for use as a food ingredient: in Canada (Health Canada, 2018), where it is authorised at an identical maximum use level in IF; in the USA (through the Generally Regarded as Safe (GRAS) scheme: GRN 571, FDA, 2015; GRN 929, FDA 2021; GRN 1014, FDA 2022), where it is authorised at higher maximum use levels of 2.0 g/L in IF and 2.4g/L in FoF, as well as being authorised in other foods for special groups and beverages; and in Australia and New

Zealand (FSANZ, 2021), where it is authorised at a higher maximum use level of 2.4 g/L in IF (for infants of age 0-12 months) as well as in formulated supplementary foods for young children.

2.1.5. Proposed use and anticipated intake

The target population for 2'-FL, as authorised in assimilated Commission Implementing Regulation (EU) 2017/2470, is the general population.

The target populations for the change in the conditions of use are infants and young children (< 3 years).

In the original authorisation for 2'-FL, the proposed use for the novel food was to be added to IF, FoF and milk-based drinks and similar products intended for young children, in combination with lacto-N-neotetraose (LNnT) at a ratio of 2:1 (EFSA NDA Panel, 2015a, 2015b). Sole use of 1.2 g/L 2'-FL was subsequently authorised in these food categories (Commission Implementing Regulation (EU) 2023/950).

The current maximum 2'-FL use levels are defined in the Union List under assimilated Commission Implementing Regulation (EU) 2017/2470 (see Table 2).

Table 2. Current permitted uses and maximum use levels for 2'-FL adapted from the List of Novel Foods (assimilated Commission Implementing Regulation (EU) 2017/2470)

Specified Food Category	Maximum Use Levels
Unflavoured pasteurised and sterilised (including UHT) milk-based products	1.2 g/L
Unflavoured fermented milk-based products	1.2 g/L beverages, 19.2 g/kg for products other than beverages
Flavoured fermented milk-based products including heat-treated products	1.2 g/L beverages, 19.2 g/kg for products other than beverages
Dairy analogues, including beverage Whiteners	1.2 g/L beverages, 12 g/kg for products other than beverages, 400 g/kg for whitener
Cereal bars	12 g/kg
Table-top sweeteners	200 g/kg
Infant formula as defined in assimilated Regulation (EU) No 609/2013	1.2 g/L (alone or in combination with up to 0.6 g/L LNnT *, at a ratio of 2:1 in the final product ready for use), marketed as such or reconstituted as instructed by the manufacturer
Follow-on formula as defined in assimilated Regulation (EU) No 609/2013	1.2 g/L (alone or in combination with up to 0.6 g/L LNnT *, at a ratio of 2:1 in the final product ready for use), marketed as such or reconstituted as instructed by the manufacturer
Processed cereal-based food and baby food for infants and young children as defined in assimilated Regulation (EU) No 609/2013	1.2 g/L for liquid food ready for use, marketed as such or reconstituted as instructed by the manufacturer, 12 g/kg for products other than beverages
Milk-based drinks and similar products intended for young children	1.2 g/L for milk-based drinks and similar products (added alone or in combination with up to 0.6 g/L LNnT *, at a ratio of 2:1 in the final product ready

Specified Food Category	Maximum Use Levels
	for use), marketed as such or reconstituted as instructed by the manufacturer
Foods for special medical purposes as defined in assimilated Regulation (EU) No 609/ 2013	In accordance with the particular nutritional requirements of the persons for whom the products are intended
Total diet replacement for weight control as defined in assimilated Regulation (EU) No 609/ 2013	4.8 g/L for drinks, 40 g/kg for bars
Bread and pasta products bearing statements on the absence or reduced presence of gluten in accordance with the requirements of assimilated Commission Implementing Regulation (EU) No 828/2014	60 g/kg
Flavoured drinks	1.2 g/L
Coffee, tea (excluding black tea), herbal and fruit infusions, chicory; tea, herbal and fruit infusions and chicory extracts; tea, plant, fruit and cereal preparations for infusions, as well as mixes and instant mixes of these products	9.6 g/L - the maximum level refers to the products ready to use
Food supplements**, excluding food supplements for infants	1.2 g/day for young children, 3.0 g/day for general population

* LNnT= lacto-N-neotetraose

** Food Supplements as defined in the Food Supplements (England) Regulations 2003/1387, the Food Supplements (Wales) Regulations 2003/1719 and the Food Supplements (Scotland) Regulations 2003/278, for the general population

This application seeks to increase the maximum use level of 2'-FL in IF and in FoF, as listed in Table 3, to better reflect real concentrations occurring in human milk. No changes to the already authorised maximum use levels for the remaining food categories are proposed.

Table 3. Proposed uses and maximum use levels for 2'-FL from the proposed change to the conditions of use.

Specified Food Category	Maximum Use Levels
Infant formula as defined in assimilated Regulation (EU) No 609/ 2013	3 g/L in the final product ready for use, marketed as such or reconstituted as instructed by the manufacturer
Follow-on formula as defined in assimilated Regulation (EU) No 609/ 2013	3.64 g/L in the final product ready for use, marketed as such or reconstituted as instructed by the manufacturer

EFSA noted that an anticipated intake for 2'-FL in children up to the age of 16 weeks is estimated to be 780 mg/kg BW/day, equivalent to 5.23 g/ day for a 6.7 kg infant. This value was calculated from the use of 2'-FL in infant formula (3 g/L) at a high consumption level of 260 ml/kg body weight/day, as established by the EFSA Scientific Committee (EFSA Scientific Committee, 2017). This value is similar to the estimated high-level daily intake for 2'-FL of 767 mg/kg BW/day in breastfed infants.

An intake assessment was conducted using the EFSA Dietary Exposure (DietEx) tool, which is based on individual data from the EFSA Comprehensive European Food Consumption Database (EFSA, 2011). The food categories taken into account in the calculations were best aligned with the proposed intended uses for each sub-population, as previously used for the assessment of a 2'-FL/DFL mixture (EFSA NDA Panel, 2019). The lowest and highest mean and lowest and highest 95th percentile estimated combined intakes (from currently authorised and proposed food uses) of 2'-FL are shown in Table 4. Estimates were also calculated using the same parameters for intake of 2'-FL from current authorised food uses (before applying the change to the conditions of use), for comparison purposes, since it was noted that the exposure estimates which supported the current authorised maximum use levels (EFSA NDA Panel, 2015a) were initially obtained using a different approach and database.

Table 4. Ranges of estimated total daily intake of 2'-FL, based on authorised conditions of use only or on combined authorised conditions of use and proposed conditions of use

Population Group *	Mean intakes (authorised uses of 2'-FL) (mg/kg BW per day)	P95** intakes (authorised uses of 2'-FL) (mg/kg BW per day)	Mean intakes (combined uses of 2'-FL) (mg/kg BW per day)	P95** intakes (combined uses of 2'-FL) (mg/kg BW per day)
Infants	51 – 438	132 – 1,377	113 – 568	291 – 1,382
Young children	116 – 398	293 – 869	123 – 438	340 – 881
Other children	45 – 198	140 – 605	44 – 198	141 – 605
Adolescents	14 – 81	52 – 233	14 – 81	52 – 233
Adults	36 – 153	95 – 337	37 – 153	100 – 337

BW= body weight
* Infants (≤ 11 months); young children (1 to < 3 years); other children (3 to < 10 years); adolescents (10 to < 18 years); adults (≥ 18 years) which includes pregnant and lactating women, elderly, and very elderly.
** P95= 95th percentile

The highest 95th percentile estimated total daily intake of 2'-FL from the combined authorised and proposed use levels for infants (1,382 mg/kg BW), and to some extent that of young children (881 mg/kg BW), are exceeding the estimated high-level daily intake for 2'-FL of 767 mg/kg BW in breastfed infants. However, they are only marginally above the updated estimated daily intakes from currently authorised use levels (1,377 and 869 mg/kg BW respectively), themselves also exceeding the estimated high-level daily intake from breast milk. The FSA and FSS noted that the intake assessment assumes the novel food is added at the maximum use levels to all the intended food categories consumed by infants, which is not a true representation of the diet of infants (particularly those above 6 months of age). Therefore, the intake of 2'-FL is unlikely to reach the estimated upper levels. In addition, it was noted that the highest daily intake level of 2'-FL

in breastfed infants on a body weight basis is exceeded in four (Bulgaria, France, Spain and Germany) out of twelve dietary surveys in the EFSA Food Consumption Database (as calculated with the DietEx tool).

Since 2'-FL is not a new novel food, EFSA concluded that the small increase in 2'-FL consumption to the infants and young children populations will only marginally increase their current estimated exposure and does not raise safety concerns (EFSA NDA Panel, 2023).

The FSA and FSS noted that in a more recent literature scoping exercise commissioned by EFSA, a maximum mean concentration of 8.40 g/L of 2'-FL in human milk (by secretor group, excluding colostrum) is identified (Malih et al., 2024); this is higher than the concentration of 4.28 g/L used in the calculation of the estimated high-level daily intake from breast milk by the applicant, and used by EFSA in the assessment of the safety of the proposed change to maximum use levels of 2'-FL in IF (EFSA NDA Panel, 2023). The highest 95th percentile estimated total daily intakes of the novel food from the combined authorised and proposed use levels for infants and for young children do not exceed the estimated high-level daily intake from breast milk (1,504 mg/kg BW/day for 1,200 mL) calculated with the maximum mean concentration of 8.40 g/L in human milk from Malih et al. (2024).

Upon review, the FSA and FSS found that this information added support to EFSA conclusions.

2.1.6. Absorption, Distribution, Metabolism and Excretion (ADME)

2'-FL as a novel food is already authorised in the EU and GB. ADME was assessed as part of the original novel food assessment, and existing conclusions on the safety of the novel food itself remain valid. The extension of use is unlikely to alter the interpretation of this information and therefore was not further reviewed.

The FSA and FSS agree with the view that the changes in the conditions of use do not alter the previous assessment of the novel food composition and specification, or the conclusion that no safety concerns have been identified.

2.1.7. Nutritional information

The novel food is primarily composed of the oligosaccharide 2'-FL, which is structurally identical to the naturally occurring, non-digestible counterpart in human breast milk.

The anticipated marginal increase in the current exposure of infants and young children as a result from the change in conditions of use does not raise concerns and is not expected to be nutritionally disadvantageous for them.

2.1.8. Toxicological information

2'-FL as a novel food is already authorised in the EU and GB. Toxicity was assessed as part of the original novel food assessment and existing conclusions on the safety of the novel food itself remain valid.

The FSA and FSS agree with the view that the changes in the conditions of use do not alter the previous assessment of the novel food composition and specification or the conclusion that no safety concerns have been identified.

2.1.8.1. Human trials

The safety of 2'-FL as produced by the applicant, and in the proposed conditions of use, is further documented by a growth and tolerance study performed by the applicant (Parschat et al., 2021), which aimed to determine the ability of an HiMO mix as part of a basic IF to support normal growth in healthy term infants compared to a standard formula lacking HiMOs.

In this multicentre, randomized, controlled, parallel-group clinical study, 341 infants from the age of less than 2 weeks old were distributed into: a control group of 116 infants exclusively breastfed, and; two randomised double-blinded groups of respectively 112 infants exclusively fed IF without HiMOs, and 113 infants exclusively fed IF containing a mixture of 5 HiMOs in proportions reflecting natural occurrence in breast milk (2'-FL (52%), 3-fucosyllactose (13%), LNT (26%), 3'-sialyllactose sodium salt (4%), 6'-sialyllactose sodium salt (5%)). The final concentration of 2'-FL in the IF with HiMOs was 2.99 g/L, similar to that proposed as a new condition of use for IF in this application.

Growth (primarily as a measure of body weight increment), tolerance (endpoints defined as stool frequency and consistency, as well as digestive tolerance and behavioural parameters) and adverse effects were monitored over 16 weeks. The authors observed similar outcomes for the IFs with or without HiMOs, and they concluded that HiMOs, including 2'-FL, at the used concentrations in a mixture are safe and well tolerated by healthy term infants during the first 4 months of their life.

EFSA considered the information provided by the study as supportive of the conclusions on the safety of 2'-FL in IF.

The FSA and FSS agree with the view that these human data are supporting the view that no safety concerns have been identified over the proposed change to the condition of use of 2'-FL in IF.

2.1.9. Allergenicity

2'-FL as a novel food is already authorised in EU and GB. Allergenicity was assessed as part of the original novel food assessment and existing conclusions on the safety of the novel food itself remain valid. Therefore, allergenicity was not further reviewed.

The FSA and FSS agree with the view that the changes in the conditions of use do not alter the previous assessment of the novel food composition and specification or the conclusion that no safety concerns have been identified.

3. Other regulators opinions and conclusions

The novel food is a purified white to ivory powder primarily composed of 2'-FL. Other saccharides (lactose, fucose, 3-fucosyllactose, fucosylgalactose, difucosyllactose, glucose, and D-galactose) are also present in small quantities in the novel food manufactured by microbial fermentation using genetically modified *E. coli* BL21 (DE3).

EFSA assessed this application for a change to the proposed use of 2'-FL, with a positive outcome (EFSA NDA Panel, 2023). The focus of the assessment by EFSA was with respect to the increase in maximum intake levels of 2'-FL resulting from the proposed increased from 1.2 g/L to 3.0 g/L in IF and from 1.2 g/L to 3.64 g/L in FoF.

The estimated daily intake of 2'-FL in high consuming (95^{th} percentile) infants (< 16 weeks of age) exclusively fed IF at the proposed maximum use level is similar to the estimated natural highest mean daily intake of 2'-FL from human milk in infants exclusively breastfed. In addition, while the estimated highest 95^{th} percentile daily intakes (mg/kg BW per day) of 2'-FL from FoF, and to a greater extent, from IF were found to be above the anticipated highest mean daily intake from breast milk, they were only marginally above existing highest 95^{th} percentile daily intakes from currently authorised maximum use levels of 2'-FL. These were also found to exceed the anticipated highest mean daily intake from breast milk, when updated using more appropriate consumption information compared to the original novel food assessment.

EFSA concluded that the proposed increased maximum levels and the resulting increased anticipated intakes did not raise concern, and that the safety of 2'-FL in IF was further supported by a human growth and

tolerance study provided by the applicant. Since 2'-FL are non-digestible and identical to HMOs found in breastmilk, EFSA also concluded that this change in the condition of use would not put consumers at a nutritional disadvantage.

Taking into account the information they reviewed, the FSA and FSS agree with the conclusions made by EFSA that the higher intake of 2'-FL from IF and FoF only marginally affects the estimated highest 95th percentile daily intake of the target populations, and does not pose a safety concern or a nutritional disadvantage under the proposed conditions of use.

4. Uncertainties and Limitations

No specific uncertainties were flagged in the assessment by EFSA. The FSA and FSS did not identify further uncertainties to be considered for this assessment.

5. FSA-FSS conclusion for GB assessment

The application has been assessed in line with 'Guidance on the preparation and presentation of an application for authorisation of a novel food' in the context of assimilated Regulation (EU) 2015/2283 (EFSA NDA Panel, 2021) and assimilated Commission Implementing Regulation (EU) 2017/2469 for the purposes of the GB assessment.

The conclusions of the EFSA opinion (EFSA NDA Panel, 2023) have been reviewed in detail by the FSA and FSS and are considered appropriate for use in GB.

In addition, the FSA and FSS note that there is extensive literature on the natural occurrence of 2'-FL in human milk (as reviewed in Soyyılmaz et al., 2021, and Malih et al., 2024), and growing literature on the tolerance of 2'-FL added to formulae (Parschat et al., 2021; Puccio et al., 2017; Riechmann et al., 2020; Vandenplas et al., 2020) which support the conclusions on the safe use of the novel food at its intended use level.

6. Outcome of the assessment

The FSA and FSS have reviewed the applicant's dossier, supporting documentation, and most notably the EFSA opinion (EFSA NDA Panel, 2023), and consider that there is sufficient evidence to conclude the assessment of the proposed conditions of use of 2'-fucosyllactose produced by genetically modified *E. coli* BL21 (DE3) without obtaining further information or conducting a further risk assessment.

The FSA and FSS conclude that 2'-FL produced by *E. coli* BL21 (DE3) is safe under the proposed change to the conditions of use. The anticipated intake levels and the proposed increase in use levels in IF and FoF for infants and

young children was not considered to be nutritionally disadvantageous. In addition, the FSA and FSS reviewed a growth and tolerance study for the use of a mixture of 5 human-identical milk oligosaccharides in IF and noted it further supported the safety of 2'-FL at the proposed maximum levels in IF.

In making this assessment, the FSA and FSS were able to rely on sufficient scientific evidence to make a conclusion on safety with no further questions to the applicant, and therefore no further risk assessment activities are necessary.

Sufficient evidence was available in the literature to give the FSA and FSS confidence about the safety of this novel food, for example, where other national food safety authorities had positively assessed the application using the same risk assessment guidance and core legal requirements which apply in GB.

Applicants provided sufficient relevant information as requested by the FSA and FSS.

The FSA and FSS review did not find any issues of divergence from the EFSA guidance (EFSA NDA Panel, 2021) or mutual approaches or new scientific issues for consideration.

There were no other specific issues that would require an assessment for the UK or the nations of the UK.

Abbreviations

Abbreviation	Definition
ADME	Absorption Distribution Metabolism and Excretion
BW	Body weight
DFL	Difucosyllactose
EC	European Commission
EFSA	European Food Safety Authority
EU	European Union
2'-FL	2'-fucosyllactose
FoF	Follow-on Formula
FSA	Food Standards Agency
FSS	Food Standards Scotland
GB	Great Britain
GRAS	Generally Regarded as Safe
HMO	Human milk oligosaccharide
HiMO	Human-identical milk oligosaccharide
IF	Infant Formula
LNnT	lacto-N-neotetraose
LNT	lacto-N-tetraose

Abbreviation	Definition
NCBI	National Centre for Biotechnology Information
NDA	Scientific panel on Dietetic products, Nutrition and Allergies
RP	Regulated Product
UK	United Kingdom

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