Bureau Nieuwe Voedingsmiddelen
Novel Foods Unit

2'-Fucosyllactose (3)

Assessment of substantial equivalence for a notification, in accordance with European Regulation 258/97 concerning novel foods and novel food ingredients

aan/to:

de Minister voor Medische Zorg
the Minister for Medical Care

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Introduction

This report documents the assessment made of the substantial equivalence of the oligosaccharide 2'-fucosyllactose (2'-FL) produced by the applicant company, FrieslandCampina Nederland BV, with a (synthetic) 2'-FL that has already been authorised in the European Union. The reference product from the company Glycom was originally approved in 2016 (EC16). Two more recently approved applications for 2'-FL preparations derived from fermentation processes were also taken into account. A substantial equivalence notification by Glycom for 2'-FL was supported by an assessment by the Food Safety Authority of Ireland (FSAI16), and a 2'-FL preparation from the company Jennewein was authorised in 2017 (EC17).

The applicant company, FrieslandCampina Nederland BV, submitted a dossier to the Medicines Evaluation Board (MEB) on 1 June 2017, together with a proposal for a notification in accordance with Article 5 of European Regulation 258/97, concerning novel foods and novel food ingredients (EC97). The applicant takes the view that a simplified authorisation procedure is appropriate because this company's 2'-FL is substantially equivalent to the 2'-FL that has already been authorised, in terms of composition, level of undesirable substances, nutritional value, metabolism and intended use. The Novel Foods Unit (NFU) has made a scientific assessment of this claim of substantial equivalence. The Unit, which is part of the Medicines Evaluation Board Agency (MEB Agency), advises the Minister of Health, Welfare and Sport regarding the safety of novel foods. The NFU performs its assessments in close consultation with the Committee on Safety Assessment of Novel Foods (VNV Committee).

The NFU bases its opinion on the data contained in the notification dossier and on the information in dossiers relating to other 2'-FL preparations. Details of the Dutch assessment procedure are given below. The VNV Committee discussed this dossier on 31 October 2017, during a plenary meeting. It concluded that a positive conclusion on substantial equivalence could be reached, if the applicant would clarify the absence of information in the dossier regarding the level of difucosyl-D-lactose in this preparation. In addition, the VNV Committee noted that the applicant had announced the completion of a 90 day oral toxicity study in rats, using its own 2'-FL preparation. While the VNV Committee would not have required such a study as part of this notification dossier, it felt that the applicant should confirm that no unexpected results were identified. At the request of the NFU, the applicant provided additional information on these matters on 17 November 2017. Earlier, on 19 October 2017, the applicant had notified the NFU about a modification of the conditions of use for 2'-FL in infant formulae and follow-on formulae . The NFU completed its assessment, taking this new information into account. Its findings are set out below.

Composition

When assessing substantial equivalence in terms of composition, the VNV Committee examines information relating to source identification, to the product specification and to the production process (HC07). Each of those topics is considered separately in this report.

Identity of the source. The 2'-FL that is the subject of this application is produced by fermentation, involving a genetically modified strain of the bacterium *E. coli* (strain: *E. coli* K12 E997). This genetically modified micro-organism (GMM) is able to produce 2'-FL, which

it then secretes into the culture medium. The product is isolated from the fermentation medium in such a way that the final product is entirely free of the production organism and its DNA. As a result, this GMM can be considered to be a processing aid, according to a report by the European Commission on the implementation of the legislation on genetically modified food and feed (EC06). Information related to the manufacturing process and a detailed description of the genetically engineered production strain was provided as an annex to the dossier. Since the applicant's 2'-FL is a highly purified product, the VNV Committee accepted that it was appropriate to use the notification procedure, even though the original reference product from the company Glycom was produced by chemical synthesis (EC16). The NFU notes that the recently authorised 2'-FL preparation from the company Jennewein is also an appropriate reference product (EC17).

Product specification. The applicant's product specification is appended as Annex I to this report. The product is a powder, consisting almost entirely of carbohydrates (at least 90% is 2'-FL). The preparation also contains limited amounts of lactose, allo-lactose, glucose, galactose, and fucose, for which separate limit values are set. The specification includes limit values for water, protein, nitrite, nitrate, and ash contents. The applicant has analysed five independently manufactured batches of 2'-FL, to show that the product complies to the proposed specification. In the dossier, the applicant presented a comparison between the analysis results, its own specification, and the specifications for two previously authorised 2'-FL preparations, demonstrating a very close resemblance. The applicant has clarified that no information on the level of difucosyl-D-lactose was included, because this substance was absent in the first experimental batches of 2'-FL, and was therefore not analysed in subsequent batches. The NFU concurs with the applicant that the novel 2'-FL can be produced according to a specification that supports substantial equivalence with authorised 2'-FL.

Production process. After fermentation, the 2'-FL is purified from the culture medium, using a number of common purification steps, mentioned in an annex to the dossier. The NFU notes that the production process resembles that described for an already authorised 2'-FL (EC17). The NFU has no reason to expect that the production process will result in an end product that would differ significantly from previously authorised 2-'FL.

Level of undesirable substances

The product specification includes limit values for aluminium, and for the heavy metals arsenic, cadmium, lead and mercury. Limit values have also been included (as microbiological parameters) for the aerobic mesophilic count, *Enterobacteriaceae*, *E. coli*, yeasts, moulds, presumptive *Bacillus cereus, Staphylococcus aureus,* sulphite reducing clostridia spores, *Clostridium perfringens*, *Salmonella,* and *Cronobacter* spp. Finally, limit values have been included for endotoxins and Aflatoxin M1, which are potential contaminants. The dossier shows that these limits are equivalent to those specified for previously authorised 2'-FL. The applicant furthermore demonstrated that the five product batches that were examined met these requirements. Therefore, the NFU has no reason to believe that the novel product differs from the reference product in terms of levels of undesirable substances or microbiological safety.

Intended use

The applicant states in the original dossier that the food categories and maximum use levels considered for the novel 2'-FL preparation are the same as mentioned in Decision 2016/376 (EC16). A change notice was added later, modifying the conditions of use for 2'-FL in infant formulae and follow-on formulae to exclude the LNnT component. The NFU notes that the intended uses correspond to the uses already authorised for 2'-FL preparations of similar purity (EC16, EC 17).

Nutritional value and metabolism

In accordance with Article 3(4) of European Regulation 258/97, information about nutritional value and metabolism is relevant for an assessment of substantial equivalence. As, in this case, the 2'-FL of FrieslandCampina Nederland BV does not differ substantially (in terms of its composition) from the 2'-FL that has already been authorised, the VNV Committee feels that its nutritional value and metabolism, too, will not differ from those of the reference product.

Conclusion

The NFU has determined that, in terms of its composition, the 2'-FL produced by the applicant, FrieslandCampina Nederland BV, is equivalent to 2'-FL preparations that have already been authorised (EC16, EC17). Accordingly, these preparations do not differ from one another in terms of nutritional value and metabolism. The NFU has no evidence of differences in the levels of relevant undesirable substances with respect to 2'-FL that has already been authorised. The novel product will also be used in the same way.

In summary, the NFU concludes that the 2'-FL supplied by the applicant company, FrieslandCampina Nederland BV, is substantially equivalent to the 2'-FL that has already been authorised, within the meaning of Article 3(4) of Regulation 258/97 concerning novel foods and food ingredients. Additional information supplied by the applicant furthermore confirmed that no unexpected results had been identified during the 90 day oral toxicity study in rats, that was performed using the applicant's 2'-FL preparation.

References

EC97 Regulation (EC) No 258/97 of the European Parliament and of the Council of 27 January 1997 concerning novel foods and novel food ingredients. Official Journal of the European Communities 1997; L43: 1-6. (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:1997:043:0001:0006:EN:PDF)

EC06 Commission of the European Communities. (2006). Report from the Commission to the Council and the European Parliament on the implementation of Regulation (EC) No 1829/2003 of the European Parliament and of the Council on genetically modified food and feed. COM (2006) 626 final.

EC16 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.

(http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32016D0376&qid=1513585317342&from=NL)

EC17 Commission Implementing Decision (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 (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32017D2201&qid=1513586740030&from=EN)

FSAI16 Food Safety Authority of Ireland: Substantial equivalence opinion on 2'-fucosyllactose. (https://www.fsai.ie/uploadedFiles/Science_and_Health/Novel_Foods/Notifications/2016%20Glycom%20Fermented%202'FL.pdf)

HC07 Health Council of the Netherlands. The safety assessment of novel foods (2).The Hague: Health Council of the Netherlands, 2007; publication no. 2007/23 (in Dutch, with Executive Summary in English, available via http://www.cbg-meb.nl/mensen/nieuwe-voedingsmiddelen/documenten/publicaties/2007/10/25/nv-advies-veiligheidsbeoordeling-deel-2).

Annex I: Product specification by the applicant

FrieslandCampina Ingredients

product specification sheet

2'-Fucosyllactose Powder

Description	Human milk oligosaccharide
Typical analysis	typical analysis on product basis: 2'-Fucosyllactose 93%, moisture 4%, lactose 1%, allo-lactose 1 %, glucose <1%, fucose <1%
Sensorial	White homogeneous powder, neutral to slightly sweet, no off flavour

Product specification

Chemical/physical	**Specification**	**CoA**	**Method of analysis**
Total moisture	max. 5%	A	ISO 760 (modified), Karl Fischer
2'-Fucosyllactose	min. 90%	A	FC-method using HPAEC-PAD
Lactose	max. 2%	A	FC-method using HPAEC-PAD
Allo-Lactose	max. 2%	A	FC-method using HPAEC-PAD
Glucose	max. 2%	A	FC-method using HPAEC-PAD
Galactose	max. 2%	A	FC-method using HPAEC-PAD
Fucose	max. 2%	A	FC-method using HPAEC-PAD
Protein	max. 0.01%	A	Bradford
Sulphated ash	max. 0.2%	A	NEN 6810 (modified)
Nitrite	max. 1 mg/kg	A	ISO 14673-2/IDF 189-2
Nitrate	max. 50 mg/kg	A	ISO 14673-2/IDF 189-2
Scorched particles	max. disc A		FC-method equivalent to ADPI 916/ISO 5739/IDF 107
pH (10%)	3.0 - 7.5	A	FC-method using NEN 3775
Aluminum	max. 4.8 mg/kg	M	FC-method using ISO 17294
Arsenic	max. 0.1 mg/kg	M	FC-method using ISO 17294
Cadmium	max. 0.01 mg/kg	M	FC-method using ISO 17294
Mercury	max. 0.05 mg/kg	M	FC-method using ISO 17294
Lead	max. 0.05 mg/kg	M	FC-method using ISO 17294
Aflatoxin M1	max. 0.2 µg/kg	M	ISO 14501/IDF 171

DOMO®

2'-Fucosyllactose Powder

Microbiological			
Aerobic mesophilic count	max. 3000 cfu/g	A	FC-method equivalent to ISO 4833
Enterobacteriaceae	absent in 10 g	A	FC-method, BPW 18h 37°C, SD, VRBG 18-24h 37°C
E. coli	absent in 10 g	A	FC-method, LMX 25h, Coli ID 24h
Yeasts	max. 10 cfu/g	A	FC-method equivalent to ISO 6611
Moulds	max. 10 cfu/g	A	FC-method equivalent to ISO 6611
Presumptive Bacillus cereus	max. 100 cfu/g	A	FC-method equivalent to ISO 7932
Staphylococcus aureus	absent in 1 g	A	ISO 6888-3, G&C 42h 37°
Sulphite reducing clostridia spores	max. 30 cfu/g	A	FC-method using IJFM 27 (1995) 185-200 Weenk
Clostridium perfringens	absent in 1 g	M	FC-method, RPM 20h 46°C, confirmation
Salmonella	absent in 25 g	A	FC-method equivalent to ISO 6579
Cronobacter spp.	absent in 25 g	A	FC-method equivalent to ISO/TS 22964
Residual endotoxins	max. 10 EU/mg	M	Eur. Ph. 2.6.14 and USP <85>
GMO-detection	negative	M	qPCR

CoA: A = analysis of each batch, M = product complies with specification based on monitoring, not mentioned on CoA

Packaging A multiple layered paper bag with polyethylene inner liner, 25 kg net.

Storage Products are best stored in original unopened packaging in clean, cool and dry conditions, away from direct sunlight and separated from strongly odorous materials.

Shelf life Products are best used before 36 months after manufacturing date when stored under the recommended conditions.

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