Bureau Nieuwe Voedingsmiddelen
Novel Foods Unit

2'-Fucosyllactose (2)

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, DuPont Nutrition & Biosciences ApS, from Denmark, 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, DuPont Nutrition & Biosciences ApS, submitted a dossier to the Medicines Evaluation Board (MEB) on 15 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 provide confirmation that the higher level of difucosyllactose in this preparation is inconsequential. After that, at the request of the NFU, the applicant provided additional information on 22 November 2017, 28 November 2017, and 16 December 2017. During that process, the applicant also provided information on the inclusion of a further purification step during the production process for 2'-FL. The NFU subsequently completed its assessment. 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 MG1655 INB3051) . 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). A risk assessment report on the GMM 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. In the course of the assessment process, the applicant has switched to a modified production process by including a further purification step. The applicant's final product specification, linked to the updated production process, is appended as Annex I to this report. The product is a powder. The dry matter consists almost entirely of carbohydrates, at least 94% of which is 2'-FL. The preparation also contains limited amounts of lactose and difucosyllactose, for which separate limit values are set. According to the dossier, small amounts of other identified carbohydrates may be present as well (3-fucosyllactose, 2'-fucosyl-D-lactulose, 2'-fucosyl-galactose, glucose, galactose, L-fucose, mannitol, sorbitol, galactitol and trihexose). The specification includes limit values for water, protein and ash contents. The applicant has analysed three batches of 2'-FL that were produced in a pilot scale facility, to show that the product complies to the proposed specification. In the dossier, the applicant presented a comparison between its own product specification and the specifications for two previously authorised 2'-FL preparations, demonstrating a very close resemblance. The maximum value for difucosyllactose is slightly higher than specified for the two authorised 2'-FL preparations, but the applicant argues that this is of no concern, by referring to difusyllactose levels in human milk. Some parameters included in the specification for the reference product from the company Glycom are production process related, and are not relevant for the present application (acetic acid, residual solvents, palladium, nickel). 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 the heavy metals arsenic, cadmium, lead and mercury. Limit values have also been included (as microbiological parameters) for the standard plate count, yeasts and moulds, Coliforms/*Enterobacteriaceae*, *Salmonella* and *Cronobacter sakazakii* (the correct name is *Cronobacter* spp.), *Listeria monocytogenes*, and *Bacillus cereus*. Finally, limit values have been included for endotoxins, Aflatoxin B1, and Aflatoxin M1, which are potential contaminants. The dossier shows that these limits are equivalent to those specified for authorised 2'-FL. The applicant furthermore demonstrated that the three 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 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), but without the LNnT component, and not including cereal bars, table-top sweeteners, bread and pasta products, flavoured drinks, coffee, tea, herbal and fruit infusions (see Annex II to this report, which was taken from the dossier). The NFU notes that the intended uses correspond to 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 DuPont Nutrition & Biosciences ApS 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, DuPont Nutrition & Biosciences ApS, 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, DuPont Nutrition & Biosciences ApS, 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.

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

Table 1: Specification of the Novel Food 2'-FL		
Parameter	**Specification**	**Method of analysis**
Source	Genetically modified strain of *Escherichia coli* K-12	
Description	a white to off-white powder	
GENERAL		
Appearance (Colour)	white to off-white	Visual
Appearance (Form)	dry powder	Visual
Appearance in solution	clear, colourless to slightly yellow	Visual
CARBOHYDRATES		
2'-Fucosyllactose (AUC)[a]	≥94%	HPAEC-PAD Internal method[b]
D-Lactose (AUC)	≤3.0%	HPAEC-PAD Internal method
Difucosyllactose (AUC)	≤2.0%	HPAEC-PAD Internal method
Other carbohydrates[c] (AUC)	≤2 %	HPAEC-PAD Internal method
CHEMICAL ANALYSIS		
Water content	≤9.0 w/w %	Colorimetric Karl-Fischer titration
Protein content	≤100 µg/g	Nanoquant (modified Bradford)
Ash[d]	≤0.5 w/w %	NMKL 173:2005, mod
Arsenic	≤0.2 mg/kg	EN 15763:2009
Cadmium	≤0.05 mg/kg	EN 15763:2009
Lead	≤0.05 mg/kg	EN 15763:2009
Mercury	≤0.1 mg/kg	EN 15763:2009
Aflatoxin M_1	≤0.025 µg/kg	EN ISO 14501 IAC-LC FLD
Aflatoxin B_1	≤1 µg/kg	IAC-LC-FLD
Endotoxins	≤300 EU/g	Ph. Eur. 2.6.14 + Interference study
GMO detection[e]	Negative	Internal protocol
Shelflife	>6 months	See annex 1
MICROBIOLOGICAL ANALYSIS		
Standard Plate Count	≤1000 CFU/g	ISO 4833-1
Yeast	≤100 CFU/g	NMKL 98
Mold	≤100 CFU/g	NMKL 98
Coliform / Enterobacteriaceae	absent in 10 g	ISO 21528-1
Salmonella	absent in 100 g	NMKL 71

Cronobacter (Enterobacter) sakazakii	absent in 100 g	ISO/TS 22964
Listeria monocytogenes	absent in 25 g	BRD 07/04-09/98
Bacillus cereus	≤10 CFU/g	NMKL 67-M

a – AUC: Area Under Curve. See the validation report in annex 2
b – Details of the analytical methods is outlined in annex 2
c - Other carbohydrates includes 3-fucosyllactose, 2'-fucosyl-D-lactulose, 2'-fucosyl-galactose, glucose, galactose, L-Fucose, mannitol, sorbitol, galactitol and trihexose.
d - Measured as total ash
e - The GMO detection involves a detection of both the *E. coli* strain and the recombinant DNA of the GMM strain (see annex 3).

Annex II: Intended use, as specified by the applicant

Table 4: Food categories and maximum use levels in the food categories	
Food categories[a]	**Maximum use level in the final food**
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 products other than beverages
Flavoured fermented milk-based products including heat- treated products	1.2 g/L beverages 19.2 g/kg 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
Infant formulae as defined in Directive 2006/141/EC	1.2 g/L in the final product ready for use, marketed as such or reconstituted as instructed by the manufacturer
Follow-on formulae as defined in Directive 2006/141/EC	1.2 g/L 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 Directive 2006/125/EC	12 g/kg for products other than beverages 1.2 g/L for liquid food 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 Directive 2006/125/EC	12 g/kg for products other than beverages 1.2 g/L for liquid food ready for use, marketed as such or reconstituted as instructed by the manufacturer
Milk-based drinks and similar products intended for young children	1.2 g/L for milk-based drinks and similar products in the final product ready for use, marketed as such or reconstituted as instructed by the manufacturer
Dietary foods for special medical purposes as defined in Directive 1999/21/EC	In accordance with the particular nutritional requirements of the persons for whom the products are intended
Foods intended for use in energy-restricted diets for weight reduction as defined in Directive 96/8/EC (only for products presented as a replacement for the whole of the daily diet)	4.8 g/L for drinks 40 g/kg for bars
Food supplements as defined in Directive 2002/46/EC, excluding food supplements for infants	3.0 g/day for general population 1.2 g/day for young children