PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2019/079962	01.11.2019	30.11.2018

International Patent Classification (IPC) or both national classification and IPC
INV. A23L33/00 A23L33/10 A61K31/702

Applicant
SOCIETE DES PRODUITS NESTLE S.A.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Fax: +31 70 340 - 3016	see form PCT/ISA/210	De Jong, Ellen Telephone No. +31 70 340-0

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2019/079962

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed.

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. ☐ This opinion has been established taking into account the **rectification of an obvious mistake** authorized by or notified to this Authority under Rule 91 (Rule 43*bis*.1(a))

3. ☐ With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, this opinion has been established on the basis of a sequence listing:

   a. ☐ forming part of the international application as filed:

      ☐ in the form of an Annex C/ST.25 text file.

      ☐ on paper or in the form of an image file.

   b. ☐ furnished together with the international application under PCT Rule 13*ter*.1(a) for the purposes of international search only in the form of an Annex C/ST.25 text file.

   c. ☐ furnished subsequent to the international filing date for the purposes of international search only:

      ☐ in the form of an Annex C/ST.25 text file (Rule 13*ter*.1(a)).

      ☐ on paper or in the form of an image file (Rule 13*ter*.1(b) and Administrative Instructions, Section 713).

4. ☐ In addition, in the case that more than one version or copy of a sequence listing has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that forming part of the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

5. Additional comments:

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	6
	No:	Claims	1-5, 7-16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Ad item V

Ad item VIII

1. Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure.

D1	US 6 946 451 B2 (KYOWA HAKKO KOGYO KK [JP]) 20 September 2005 (2005-09-20)
D2	US 9 636 367 B2 (NESTEC SA [CH]) 2 May 2017 (2017-05-02)
D3	US 2016/296585 A1 (BLANCHER FLORENCE [CH] ET AL) 13 October 2016 (2016-10-13)
D4	WO 2017/129639 A1 (NESTEC SA [CH]) 3 August 2017 (2017-08-03)
D5	US 2017/295838 A1 (DESTAILLATS FREDERIC [CH] ET AL) 19 October 2017 (2017-10-19)
D6	WO 2017/129650 A1 (NESTEC SA [CH]) 3 August 2017 (2017-08-03)
D7	US 2016/296543 A1 (BRASSART DOMINIQUE [CH] ET AL) 13 October 2016 (2016-10-13)
D8	WO 2018/215573 A1 (NESTEC SA [CH]) 29 November 2018 (2018-11-29)
D9	US 2018/333426 A1 (CHICHLOWSKI MACIEJ [US] ET AL) 22 November 2018 (2018-11-22)
D10	US 2018/104267 A1 (BUCK RACHAEL [US] ET AL) 19 April 2018 (2018-04-19)

D1 (US6946451) discloses an insulin secretion promoter comprising 2FL (Example 1, claims 1-18). In Example 6 a milk powder for infants is prepared, containing 0.3% by weight of 2FL. The composition may also comprise LNnT, 3SL and 6SL (claim 1). It was shown that the serum insulin concentration improved (Tables 1-6, 8, 10, 11).

D2 (US9636367) discloses (claims 1-19, Table 2) a method for increasing insulin sensitivity and/or reducing insulin resistance in an infant who is predisposed for developing insulin resistance, the method comprising administering at least one LC-PUFA, at least one probiotic and an oligosaccharide mixture containing 2FL, LNnT and 3SL or 6SL.

D3 (US2016/0296585) discloses a nutritional composition for use in treatment, prevention and/or reducing the risk of a metabolic syndrome disorder appearing later in life, wherein the composition comprises more than 70% casein based on the total protein content. (claims 1-15). In par.134 reference is made to the determination of pancreatic insulin (appears to be similar to the method of present page 34 l.14-16).

Infant formula with the same amounts of fucosylated and N-acetylated oligosaccharides (and 3SL, 6SL) for various uses were known in the art, see D4 (WO2017/129639) for use in preventing and/or treating a health disorder by increasing GLP-1 secretion, D5 (US2017/0295838) for reducing cardiovascular diseases, risk of obesity, D6 (WO2017/129650) for use in reducing and/or avoiding excessive fat mass accumulation, D7 (US2016/0296543) for preventing/treating allergies, D8 (WO2018/215573) for the use of improving memory, D9 (US2018/0333426) for modulating gut microbiota and improving cognitive function and stimulating neuronal development, D10 (US2018/0104267) for stimulating immune activity.

2. In the description (p.3 l.4-26, p.26 l.5-p.27 l.16) a difference is made between the biosynthesis and secretion of insulin by the pancreas. Assumptions are made as to long-term effects. In Example 3 a study is done on rats, wherein the effects of different diets on insulin content of the pancreas are compared. On p.34 l.13-16 it is explained that:

Rats were sacrificed at day 57 (postnatal day 57 = p57) after a 6-hr fasting period and pancreas was dissected and its insulin content was extracted using a solution acid ethanol and quantified using an Ultra Sensitive Insulin ELISA kit (CrystalInc., Downer Grove, IL, USA) with and inter assay CV of 4.0%.

It was shown that with a diet with 2FL with or without LNnT the amount of insulin per g of pancreatic tissue was significantly higher than with the control diet (p.35 l.4-20). The conclusion that the biosynthesis of insulin is enhanced is valid. An assumption is made

that this boosted biosynthesis of insulin implies an enhanced development or maturation of the pancreas (p.35 l.7-20). Another assumption is made that there are long-term effects (p.35 l.22-26).

Insulin biosynthesis and insulin secretion are both regulated by glucose levels and other nutrients (see present p.3 l.4-12). However, it is to be noted that in the present examples the serum insulin and glucose concentrations were not measured. Therefore, any effect on glucose management is unknown. Claim 9 is therefore unlikely to be sufficiently disclosed.

Furthermore, a direct comparison with prior art documents is not possible. It is assumed that whenever an increased insulin secretion is demonstrated in the prior art, an enhancement of the biosynthesis is implicit, in view of the same regulation mechanism. D1 and D2 are thus considered to anticipate present claims 1-5 and 7-16.

The subject-matter of claim 6, referring to the amount of of N-acetylated oligosaccharide, does not involve an inventive step in view of e.g. D5, which already teaches the use of the same amount for a similar purpose.

The use of the composition containing fucosylated and N-acetylated oligosaccharides (and 3SL, 6SL) for reducing the risk of type-2 diabetes and/or obesity (see present claim 9) was already known in the art, see D1, D2, D4-D6. It therefore appears that the present claims describe the underlying mechanism for this medical effect.

3. Clarity

3.1 Claims 2 and 6 are unclear because the indicated amounts are confusing; "0.05-3" appears to be in contradiction with "at least 0.2" The same applies to the other amounts.

3.2 The subject-matter of claim 8 is unclear because it implies another mechanism underlying the suggested pancreatic development or maturation apart from the enhancement of the level of biosynthesis of insulin. No such other mechanism is disclosed in the present description. See Example 3, wherein it was shown that with a diet with 2FL with or without LNnT the amount of insulin per g of pancreatic tissue was significantly higher than with the control diet.

3.3 Claim 6 should refer to "any of claims 4 or 5" because "said N-acetlyated oligosaccharide" is not mentioned in claims 1-3.

Similarly, claim 16 should refer to "any of claims 4 to 15".