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Datasheet for the decision of 27 October 2020

Case Number: T 2788/17 - 3.3.09

Application Number: 12707135.5

Publication Number: 2672844

IPC: A23L1/30, A23L1/308, A23L1/09

Language of the proceedings: EN

Title of invention:
MODULATION OF GROWTH OF BIFIDOBACTERIA USING A COMBINATION OF OLIGOSACCHARIDES FOUND IN HUMAN MILK

Patent Proprietor:
Société des Produits Nestlé S.A.

Opponent:
N.V. Nutricia

Headword:
Prebiotic formulation of human milk oligosaccharides

Relevant legal provisions:
EPC Art. 53(c), 56, 83, 123(2)
RPBA Art. 12(4)
RPBA 2020 Art. 25(2)

Keyword:
Main request:
Subject-matter excluded from patentability - (no)
Sufficiency of disclosure - (yes)
Inventive step - (yes)

Decisions cited:
T 0110/18

Catchword:

Europäisches Patentamt
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Beschwerdekammern

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Case Number: T 2788/17 - 3.3.09

D E C I S I O N
of Technical Board of Appeal 3.3.09
of 27 October 2020

Appellant: (Opponent)	N.V. Nutricia Eerste Stationsstraat 186 2712 HM Zoetermeer (NL)
Representative:	Nederlandsch Octrooibureau P.O. Box 29720 2502 LS The Hague (NL)
Respondent: (Patent Proprietor)	Société des Produits Nestlé S.A. Entre-deux-Villes 1800 Vevey (CH)
Representative:	Plougmann Vingtoft a/s Strandvejen 70 2900 Hellerup (DK)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 19 October 2017 rejecting the opposition filed against European patent No. 2672844 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Haderlein
Members:	A. Veronese
	F. Blumer

Summary of Facts and Submissions

I. This decision concerns the appeal filed by the opponent against the decision of the opposition division to reject the opposition filed against European patent No. 2 672 844 B1.

II. With its notice of opposition, the opponent had requested revocation of the patent in its entirety on the grounds under Article 100(a) (combined with Articles 53(c) and 56 EPC), and 100(b) EPC.

III. Claim 1 and 11 of the granted patent read as follows:

"*1. A prebiotic formulation for oral administration to a human comprising 2'-fucosyllactose, 3'-sialyllactose and 6'-sialyllactose, wherein the amount by weight of the 3'-sialyllactose is at least as great as the amount of the 2'-fucosyllactose.*"

"*11. A method for modulating or stimulating the growth of Bifidobacteria in the human intestines comprising orally administering to a human the formulation of any of claims 1-10.*"

IV. The documents submitted during the opposition proceedings included:

D1: Barboza M. et al., Applied and Environmental Microbiology, 2009, vol. 75(23), pp. 7319-7325

D2: Falony G. et al., Applied and Environmental Microbiology, 2009, vol. 75(2), p. 454-461

D4: Tadashi I. et al., Bioscience Biotechnology and Biochemistry, 1994, vol. 58(9), pp. 1720-1722

D5: WO 2009/113861 A2

D7: US 2010/0260720 A1

D8: Ward R. E. et al., Molecular Nutritional and Food Research, 2007, vol.51, 1398-1405

D9: Martin-Sosa S. et al., Journal of Dairy Science, 2003, vol. 86, pp.52-59

D13: WO 01/60346 A2

D14: WO 2007/051475 A1

D15: WO 2005/055944 A2

D16: WO 2007/114696 A1

D17: Experimental report filed by the patent proprietor by letter dated 12.01.2016

D18: Asakuma S. et al., The Journal of Biological Chemistry, 2011, vol. 286(40), pp. 34583-34592

V. In its decision, the opposition division found that:

- Claim 11 was not directed to a therapeutic method of treatment according to Article 53(c) EPC.

- The claimed invention was sufficiently disclosed.

- The claimed subject-matter involved an inventive step. The claimed formulation differed from that disclosed in D13, the closest prior art, in that it contained 2'-fucosyllactose. The underlying problem was how to modify the formulation of D13 to stimulate the growth of *Bifidobacterium bifidum*. The prior art did not hint at the claimed solution.

VI. In the statement setting out the grounds of appeal, the appellant requested that the decision rejecting the opposition be set aside and that the patent be revoked in its entirety. Two further documents were referred to and enclosed with the statement:

D21: Sela D.A. et al., Proceedings of the National Academy of Sciences of the United States of America, 2008, vol. 105(48), pp. 18964-18969

D22: Katayama T. et al., Journal of Bacteriology, 2004, vol. 186(15), pp.4885-4893

VII. In the reply to the statement setting out the grounds of appeal, the patent proprietor (respondent) requested that the appeal be dismissed or, alternatively, that the patent be maintained on the basis of one of auxiliary requests 1 to 4 enclosed with the statement. Furthermore, it requested that D21 and D22 not be admitted into the appeal proceedings.

VIII. The parties were summoned to oral proceedings. In a written communication issued in preparation for the hearing, the board expressed the preliminary opinion that claim 11 of the main request and auxiliary requests 1 and 2 did not comply with the requirements of Articles 53(c) EPC and/or 83 EPC. The claims of auxiliary request 3 were considered to meet these requirements and those of Article 56 EPC.

IX. In a letter in reply to the board's communication, dated 31 July 2020, the respondent withdrew the main request and auxiliary requests 1 and 2 and filed a main request corresponding to the previously filed auxiliary request 3. It also withdrew the request for oral proceedings, contingent on the new main request being considered allowable.

X. Claim 1 of the main request corresponds to granted claim 1, whereas claim 11 reads as follows:

"11. A formulation according to any of claims 1-10 for use in modulating or stimulating the growth of Bifidobacterium bifidum, Bifidobacterium breve and Bifidobacterium infantis in the human intestines by orally administering to a human said formulation."

XI. The board issued a second communication dated 27 August 2020 in preparation of the oral proceedings. On the same day, the appellant withdrew its request for oral proceedings and requested that a decision be taken on the file as it stands. The oral proceedings were then cancelled.

XII. The arguments of the appellant relevant for the present decision were as follows.

- Granted claim 11 encompassed subject-matter excluded from patentability under Article 53(c) EPC.

- There was no evidence that the claimed formulation induced the growth of bifidobacteria *in-vivo*. The *in-vitro* tests described in the patent and D17 did not reproduce the environment in the human intestine. This was confirmed by D1 and D2. Furthermore, D17 and D21 provided evidence that the claimed formulation did not promote the growth of certain bifidobacteria types. These non-working embodiments confirmed that the invention defined in claim 11 could not be carried out across the claimed scope.

- The claimed subject-matter did not involve an inventive step over a combination of D13, the closest prior art according to the impugned decision, with D8 and/or D22. Starting from D13,

which disclosed a formulation comprising 3'-sialyllactose (3'-SL) and 6'-sialyllactose (6'-SL), but not 2'-fucosyllactose (2'-FL), the underlying problem was modifying the formulation of D13 to stimulate the growth of *Bifidobacterium bifidum*. D8 and D22 taught that 3'-FL promoted the growth of this bacterium, hinting at including this compound in the formulation. Analogous conclusions could be arrived at combining: D4 with D8 and/or D22; D7 with D13; D21 with D13 or D4; D9 with D10, D11 and/or D12; D5, D13, D14, D15, D16 with common knowledge or with D10, D11 and/or D12.

XIII. The arguments of the respondent relevant for the present decision were as follows.

- Neither granted claim 11 nor the reworded clam 11 of the main request infringed Article 53(c).

- Claim 1 related to a prebiotic formulation comprising commercially available oligosaccharides, which could be prepared without difficulties following the instructions given in the patent. The *in-vitro* tests in the patent made it plausible that the claimed formulation promoted bacterial growth *in-vivo.* There was no evidence to the contrary, let alone in D1 and D2. In fact, these documents confirmed the significance of *in-vitro* tests. Furthermore, the claimed invention did not require the formulation to promote the growth of all bifidobacteria types.

- The claimed subject-matter involved an inventive step over D13, the closest prior art. The claimed formulation differed from that disclosed in D13 in that it comprised 2'-FL. The underlying problem was

modifying the formulation of D13 to further stimulate the growth of *Bifidobacterium bifidum*. None of the other prior art documents, and in particular D8 and D22, hinted at the claimed solution, i.e. at including 2'-FL in the formulation. The same conclusions could be arrived at starting from the other documents proposed by the appellant as closest prior art.

XIV. The final requests.

The appellant requested that the decision rejecting the opposition be set aside and that the patent be revoked in its entirety.

The respondent requested that the patent be maintained on the basis of the main request filed by letter dated 31 July 2020.

Reasons for the Decision

1. *Subject-matter excluded from patentability*

1.1 Claim 11 of the main request was reworded to define a formulation comprising certain oligosaccharides for use in modulating or stimulating the growth of specific bacteria in the intestine of a human. Since it is directed to a product for a specific use, the appellant's objection that granted claim 11, which was directed to a method, infringed Article 53(c) EPC, is no longer applicable.

2. *Sufficiency of disclosure*

2.1 The claimed invention relates to a prebiotic formulation for oral administration to a human

comprising three specific oligosaccharides (claim 1) and its use to modulate or stimulate the growth of *Bifidobacterium bifidum*, *Bifidobacterium breve* and *Bifidobacterium infantis* (claim 11).

2.2 The patent in suit describes in detail how to prepare a formulation for oral administration comprising 2'-FL, 3'-SL and 6'-SL: see paragraphs [0014] to [0024]. It was not disputed that, as stated on paragraph [0025], these oligosaccharides were well known and commercially available before the relevant date.

2.3 Furthermore, example 1 of the patent describes tests showing that the growth of *Bifidobacterium bifidum*, *infantis* and *breve* can be stimulated *in-vitro* by at least one of the three oligosaccharides in the claimed composition. In particular, it is shown that:

- the growth of *Bifidobacterium bifidum* is promoted by 2'-fucosyllactose (2'-FL)

- the growth of *Bifidobacterium infantis* is promoted by 2'fucosyllactose, 3'-sialyllactose (3'-SL) and 6'-sialyllactose (6'-SL)

- the growth of *Bifidobacterium breve* is promoted by 3'-sialyllactose (3'-SL)

2.4 These results are confirmed in the experimental report D17.

2.5 The appellant raised several concerns as to whether these effects could be achieved *in-vivo*. However, beside arguing that *in-vitro* results are not necessarily conclusive, the appellant has not presented any concrete evidence that the claimed composition is

not suitable for promoting the growth of the relevant bifidobacteria types *in-vivo,* in the human intestine. According to the appellant, D1 and D2 confirmed that the consequence of competition between the bacteria in the intestine had still to be determined and that caution was needed when extrapolating *in-vitro* results. Nonetheless, the language used by the authors of D1 and D2 is prudent and reflects sound scientific behaviour. Furthermore, this language in no way discards the *in-vitro* results shown in these documents for being insignificant. To the contrary, the authors consider *in-vitro* tests as a suitable tool for predicting the suitability of the relevant agents for inducing bacterial growth *in-vivo* (see the conclusions in the last paragraph on page 7325 of D1 and the right-hand column of page 458 of D2).

2.6 The appellant has also argued, referring in particular to granted claim 11, that the claimed formulation was not suitable for promoting the growth of certain types of bifidobacteria. It noted that, as shown in D17, none of the claimed oligosaccharides promoted the growth of *Bifidobacterium longum*, that 2'-FL and 6'-SL did not promote the growth of *Bifidobacterium breve*, and that 3'-SL and 6'-SL did not promote the growth of *Bifidobacterium bifidum*. The appellant also noted that D21 showed that a composition comprising these three compounds did not stimulate the growth of *Bifidobacterium longum and adolescentis.* Thus, the claimed invention could not be carried out across the entire scope claimed.

2.7 These arguments are not persuasive either. In the first place, claim 11 of the main request does not encompass, as granted claim 11, the treatment of *Bifidobacterium longum* and *adolescentis*. Furthermore, as discussed

above, the available results show that the growth of *Bifidobacterium bifidum*, *infantis* and *breve* is stimulated by at least one of the oligosaccharides in the claimed formulation. Accordingly, in the absence of any evidence to the contrary, it is credible that a formulation comprising these oligosaccharides is suitable for inducing, *in-vivo*, the growth of *Bifidobacterium bifidum*, *infantis* and *breve*, and, as a consequence, a prebiotic effect.

2.8 For these reasons, the board arrives at the conclusion that, relying on the information presented in the patent and the common general knowledge at the filing date, the skilled person would have been able to prepare a prebiotic formulation as defined in claim 1 and use it in the method of claim 11. Accordingly, the claimed invention is sufficiently disclosed (Article 83 EPC).

2.9 The respondent requested that D21 not be admitted in the appeal proceedings. In view of the arguments presented above (see point 2.7), it is clear that the teaching of this document is not relevant and does not influence the outcome of the proceedings with respect to sufficiency of disclosure. Thus, there is no reason to discuss its admissibility.

3. *Inventive step*

The closest prior art

3.1 The claimed invention relates to the preparation of a prebiotic formulation for oral administration comprising oligosaccharides found in human milk and also the use of this formulation for stimulating the growth of the *Bifidobacterium* types indicated in

claim 11 in the human intestine. Accordingly, a document which focuses on the preparation of a formulation comprising these types of oligosaccharides and its use to achieve this same effect has to be selected as the closest prior art.

3.2 In the decision under appeal, the opposition division considered that D13 is the closest prior art. The appellant proposed a number of other documents (D4, D5, D7, D9, D14, D15, D16 and D21) as alternative starting points for assessing inventive step. It is therefore necessary, to correctly apply the problem/solution approach, to establish, in the first place, which of these documents is the closest prior art.

3.3 Among the aforementioned documents, only D13 and D4 focus specifically on, and present experimental evidence relating to, the use of formulations comprising oligosaccharides from human milk for stimulating the growth of bifidobacteria in the intestine.

3.4 D13 discloses a nutritional formulation comprising 3'-SL and 6'-SL and its use for promoting the growth of *Bifidobacterium infantis* and *lactis* in the human intestine. The board does not see any reason to deviate from the opposition division's choice of this document as the closest prior art. D13 is also better than D4 as the closest prior art because D4 refers generically to "sialyllactose (SL)", without indicating whether 3'-SL or 6'-SL or their mixture was meant with this wording. Furthermore, the tests shown in D4 were conducted under special conditions, in the presence of a large excess (35 to 3500 times) of lactose, which is another substrate for bacterial growth.

3.5 As far as the other documents are concerned, the appellant has not explained why these should represent better starting points than D13, the closest prior art according to the impugned decision. Furthermore:

- D7 relates to a treatment involving the administration of a combination of bifidobacteria probiotics and prebiotics. Since bacteria are administered to the subject, the invention differs substantially from the claimed one.

- D9 does not mention promotion of the growth of bifidobacteria, let alone the specific types mentioned in claim 11.

- Concerning D5, D14, D15 and D16, mere passing reference was made by the appellant to some passages of these documents, without further discussion as to their relevance and suitability as the closest prior art. Furthermore, these documents appear *prima facie* more remote than the previous ones, for example, because they do not focus on the growth of the bifidobacteria, let alone the types relevant according to the claimed invention.

- D21 was filed for the first time in appeal and relied on to formulate a new inventive step attack. No reasons were given, and the board does not see any, for presenting this new attack only at this stage. Thus, this attack is not admitted into the appeal proceedings (Article 12(4) RPBA 2007, and Article 25(2) RPBA 2000), regardless of whether D21 is admitted into the proceedings.

3.6 For these reasons, it is concluded that D13 is the closest prior art.

The technical difference and the technical effect

3.7 The parties agree that the claimed formulation differs from that disclosed in D13 in that it comprises 2'-FL, in the claimed amount, in addition to the other two oligosaccharides derived from milk (HMOs) 3'-SL and 6'-SL. They also concur that the effect induced by the presence of 2'-FL is that the composition stimulates the growth of *Bifidobacterium bifidum*. The results shown in the patent, confirmed by D17, make it indeed credible that the claimed formulation, which comprises all three HMOs, is suitable for inducing this effect (see points 2.2 to 2.7 above).
Furthermore, as noted by the respondent, D17 shows that 3'-SL and 6'-SL (comprised in the formulation of D13) induce the growth of *Bifidobacterium breve* and *infantis* but not *Bifidobacterium bifidum*. This confirms that the presence of 2'-FL is essential for promoting the growth of this bacterium.

The technical problem

3.8 The parties agree that the underlying objective technical problem is how to modify the formulation disclosed in D13 to further stimulate the growth of *Bifidobacterium bifidum*.

Non-obviousness of the claimed solution

3.9 What has to be decided is whether, taking into account the teaching of the prior art, the proposed solution, namely the addition of 2'-FL in the specified amount to the formulation of D13, would have been obvious for the skilled person.

3.10 The appellant argued that D8 and D22, which disclose studies investigating the fermentability of some HMOs by different strains of bifidobacteria, would have inclined the skilled person towards the proposed solution.

The board does not agree.

3.11 D8 describes a study aimed at determining the ability of different strains of bifidobacteria to ferment HMOs. The experiments were carried out using a mixture of HMOs. While it may be assumed that the mixture contained 2'-FL, a large number of other HMOs was also present. This renders it impossible to assess the individual effect of the different HMOs and, in particular, of 2'-FL. Furthermore, as noted by the respondent, figure 1B on page 1400 shows that *Bifidobacterium bifidum* is the bacterium which grows less on HMOs substrates. From this result, the skilled person would not have any sound reason to expect 2'-FL to stimulate the growth of this bacterium. Besides this, D8 concludes on page 1404, left column, last paragraph, that only *Bifidobacterium longum* and *infantis* were able to grow substantially on HMOs as substrate. Thus, D8 does not hint at the proposed solution.

3.12 Taking into account the concentration of the HMOs used in tests described in D17 and referring to the passage on page 1400, right-hand column, the appellant tried to demonstrate that it could be inferred from D8 that 2'-FL stimulated the growth of *Bifidobacterium bifidum*. However, for the reasons given above, these arguments are not convincing.

3.13 D22 teaches that, despite the fact that *Bifidobacterium bifidum* cannot ferment L-fucose, this bacterium expresses alpha-L-fucosidase, the enzyme which degrades 2'-FL. Nonetheless, D22 is completely silent as to whether 2'-FL can stimulate the growth of *Bifidobacterium bifidum*. The ability to degrade 2'-FL does not necessarily result in an increased growth rate. As noted by the respondent, in referring to D4 and D18, the degradation of 2'-FL could possibly promote the growth of commensal bacteria but not necessarily *Bifidobacterium bifidum*. Thus, D22 does not in any way hint at the proposed solution either.

3.14 The respondent has requested that D22, filed for the first time in appeal, not be admitted into the appeal proceedings. In view of the conclusions above, it is clear that the teaching of this document is not relevant and does not influence the outcome of the proceedings with respect to sufficiency of disclosure. Thus, there is no reason to discuss its admissibility.

3.15 For these reasons, it is concluded that the prior art does not in any way hint at adding 2'-FL to the formulation disclosed in D13, let alone in the specified amount. Even assuming that the skilled person could have considered adding this compound, they would not have done this with a reasonable expectation of solving the underlying technical problem.

3.16 Accordingly, the claimed subject-matter involves an inventive step (Article 56 EPC).

4. *Reimbursement of the appeal fee*

The appellant withdrew its request for oral proceedings on the same day as the date of the board's second

communication in preparation of the oral proceedings (see XI above), i.e. within the time limit required in accordance with Rule 103(4)(c) EPC (see T 110/18, reasons 7). No oral proceedings took place. Thus the requirements for reimbursement of 25% of the appeal fee are met.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the opposition division with the order to maintain the patent as amended according to the claims of the main request filed with the letter dated 31 July 2020 and a description to be adapted thereto.

3. The appeal fee is reimbursed at 25%.

The Registrar: The Chairman:

D. Grundner A. Haderlein

Decision electronically authenticated