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Datasheet for the decision of 18 May 2021

Case Number: T 1544/16 - 3.3.09

Application Number: 07786738.0

Publication Number: 2031986

IPC: A23L1/305, A61K38/01, A61P37/08

Language of the proceedings: EN

Title of invention:
INDUCTION OF TOLERANCE TO EGG PROTEINS

Patent Proprietor:
Société des Produits Nestlé S.A.

Opponents:
Hill's Pet Nutrition, Inc.
N.V. Nutricia

Headword:
Induction of tolerance to egg proteins/NESTLÉ

Relevant legal provisions:
EPC Art. 56, 84, 123(2)

Keyword:
Inventive step - main request (no) - auxiliary requests 1A to 1C and 2 (no)
Amendments - added subject-matter (yes) - auxiliary requests 3, 4A, 5A, 6A to 6D, 7A to 7D and 8A to 8D
Claims - clarity - auxiliary requests 9A to 9E (no)

Decisions cited:
G 0003/14, T 0230/07, T 1661/16

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Case Number: T 1544/16 - 3.3.09

D E C I S I O N
of Technical Board of Appeal 3.3.09
of 18 May 2021

Appellant: (Opponent 2)	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:	Santarelli 49, avenue des Champs-Elysées 75008 Paris (FR)
Party as of right: (Opponent 1)	Hill's Pet Nutrition, Inc. 400 Southwest 8th Street Topeka, Kansas 66603 (US)
Representative:	Daniels, Jeffrey Nicholas Page White & Farrer Bedford House John Street London WC1N 2BF (GB)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 4 May 2016 rejecting the opposition filed against European patent No. 2031986 pursuant to Article 101(2) EPC.**

Composition of the Board:

Chairman	A. Haderlein
Members:	F. Rinaldi
	D. Rogers

Summary of Facts and Submissions

I. This decision concerns the appeal filed by opponent 2 (appellant) against the decision of the opposition division to reject the oppositions against European patent No. 2 031 986.

II. In the notice of opposition, opponents 1 and 2 had requested revocation of the patent in its entirety based on, *inter alia*, Article 100(a) EPC (lack of inventive step).

III. The documents cited during opposition proceedings include:

D3: R. Fritsché et al., "Induction of systemic immunologic tolerance to β-lactoglobulin by oral administration of a whey protein hydrolysate", The Journal of Allergy and Clinical Immunology, 100(2), August 1997, 266-273

D11: I. B. Nasser et al., "The [173-196] fragment of ovalbumin suppresses ovalbumin-specific rat IgE responses", International Immunopharmacology, 3, 2003, 1569-1579

IV. The opposition division decided to reject the oppositions. Among other things, it decided that the subject-matter of claim 1 involved an inventive step.

V. In reply to the statement setting out the grounds of appeal (dated 27 January 2017), the respondent (patent

proprietor) filed the first to ninth auxiliary requests.

By letter dated 9 April 2020, it replaced the fourth, fifth, seventh and eighth auxiliary requests with auxiliary requests AR 4A, 5A, 7A and 8A.

Furthermore, by letter dated 16 April 2021, it filed auxiliary requests AR 1B, 1C, 6B, 6C, 6D, 7B, 7C, 7D, 8B, 8C, 8D, 9B, 9C, 9D and 9E. Moreover, the first, second, third, sixth and ninth auxiliary requests were renamed as auxiliary requests AR 1A, 2, 3, 6A and 9A.

The wording and order of requests is set out below (see points VII and X).

VI. Opponent 1 (party as of right) has not filed any requests and did not take an active part on appeal.

VII. Wording of the relevant requests

Claim 1 of the main request (patent as granted) reads:

"The use of enzymatically hydrolysed egg proteins with a degree of hydrolysis between 15 and 28% in the manufacture of a composition for induction of oral tolerance to egg proteins in a mammal."

Claim 1 of auxiliary requests AR 1A, 1B, 1C and 2 is based on claim 1 of the main request, in which the degree of hydrolysis is further restricted:

- 18 to 25% (auxiliary request 1A)
- 20 to 28% (auxiliary request 1B)
- 20 to 25% (auxiliary request 1C)
- 23 to 25% (auxiliary request 2)

In claim 1 of auxiliary requests AR 3 and 6A to 6D, the following feature is added to claim 1 of the main request:

", wherein the egg proteins have been hydrolysed using the bacterial serine endoprotease subtilisin"

Furthermore, in auxiliary requests AR 6A to 6D, the degree of hydrolysis is restricted.

In claim 1 of auxiliary requests AR 4A and 7A to 7D, the following feature is added to claim 1 of the main request:

", wherein the egg proteins have been hydrolysed by a two stage enzymatic hydrolysis by heating pasteurised liquid whole egg to 60 to 65°C for about ten minutes, then cooling to about 55°C, adding the protease, maintaining the mixture at about 55°C for at least two hours, then raising the temperature to 70° to 75°C, holding it there for about 10 minutes, cooling the mixture to about 55°C, adding a further amount of enzyme, maintaining the mixture at about 55°C for at least a further two hours, then raising the temperature to between 85°C and 95°C and holding it there for about for [sic] a period of up to 30 minutes"

Furthermore, in auxiliary requests AR 7A to 7D, the degree of hydrolysis is restricted.

Claim 1 of auxiliary requests AR 5A and 8A to 8D is based on claim 1 of auxiliary request 4A with the term "adding the protease" being replaced with the term "adding the bacterial serine endoprotease subtilisin".

Furthermore, in auxiliary requests AR 8A to 8D, the degree of hydrolysis is restricted.

In claim 1 of auxiliary requests 9A to 9E, the following feature is added to claim 1 of the main request:

", wherein the egg proteins have been hydrolysed by a two stage enzymatic hydrolysis starting from pasteurised liquid whole egg"

Furthermore, in auxiliary requests AR 9B to 9E, the degree of hydrolysis is restricted.

VIII. The appellant's arguments relevant to the present decision may be summarised as follows.

Main request and auxiliary requests AR 1A to 1C and 2

D11 was the closest prior art, and the skilled person would have applied the teaching of D3 to arrive at the subject-matter of claim 1. The opposition division was wrong in assessing that the skilled person would not have applied the teaching of D3. The variation of the degree of hydrolysis involved routine experiments within the teaching of D3.

Remaining auxiliary requests

The remaining auxiliary requests involved, among other things, added subject-matter (auxiliary requests AR 3, 4A, 5A, 6A to 6D, 7A to 7D and 8A to 8D) or unclear subject-matter (auxiliary requests AR 9A to 9E).

IX. The respondent's arguments relevant to the present decision may be summarised as follows.

Main request and auxiliary requests 1A to 1C and 2

The invention involved an inventive step. D11 was not the closest prior art. D3 related to milk proteins, not egg proteins, and therefore did not belong to a neighbouring field. Furthermore, the skilled person would have found no indication to provide hydrolysed egg proteins with the degree of hydrolysis specified in claim 1. This applied all the more to the restricted ranges of auxiliary requests AR 1A to 1C and 2.

Remaining auxiliary requests

The subject-matter of the auxiliary requests was disclosed in the application as filed. The skilled person would have no difficulty in understanding the claims. Furthermore, they would also have referred to the description to interpret the claims.

X. Final requests

The appellant's final requests were that the decision under appeal be set aside and that the patent be revoked.

The respondent's final requests were, as a main request, that the appeal be dismissed (equivalent to the patent being maintained as granted) or, alternatively, that the patent be maintained on the basis of one of auxiliary requests AR 1A to 1C, AR 2, AR 9A to 9E, AR 4A, AR 7A to 7D, AR 3, AR 5A, AR 6A to 6D and AR 8A to 8D. It requested that the auxiliary requests be considered in this order.

Reasons for the Decision

1. *The patent in suit*

The patent in suit relates to the use of hydrolysed egg proteins to induce oral tolerance to intact egg proteins in mammals likely to be allergic to eggs. Oral tolerance involves administration of antigens through the oral route to prevent subsequent systemic immune responses to the same antigen given in an immunogenic form (paragraphs [0001] and [0004]). The solution entails the use of enzymatically hydrolysed egg proteins with a degree of hydrolysis between 15 and 28%.

2. *Main request - inventive step*

2.1 The appellant contested the opposition division's decision that the subject-matter of claim 1 (wording, see point VII) involved an inventive step. It argued that the subject-matter of claim 1 lacked inventive step, for instance starting from D11 as the closest prior art. It disagreed in particular with the opposition division's reasoning in the decision under appeal (page 9) that the skilled person "would not have been lead to the present invention, since the end result in terms of sufficiently low residual allergenicity, and sufficiently high capacity to induce oral tolerance at the DH [degree of hydrolysis - note by the board] required by the present claims, would not have been certain".

2.2 At the oral proceedings before the board, the respondent stated that, in its view, D11 was not the

closest prior art, but it did not provide further explanations.

However, D11 relates to inducing oral tolerance to a native egg protein (ovalbumin) using egg protein hydrolysate. The patent in suit addresses at least a similar technical problem. In view of this alone, D11 is a promising springboard for assessing inventive step and is considered the closest prior art.

2.3 The closest prior art D11

2.3.1 In its abstract, D11 discloses that:

- peptides and protein hydrolysates are tools for the induction of tolerance or regulation of targeted B or T cell responses
- in vitro, peptides are produced by enzymatic digestion and chemical hydrolysis of proteins
- the publication investigates the potential of CNBr-hydrolysed ovalbumin fractions to induce oral tolerance to native ovalbumin
- CNBr-hydrolysis releases several peptides with stimulatory effect on native ovalbumin-specific T cells
- a peptide fragment which induces oral tolerance to native ovalbumin is identified

2.3.2 Furthermore, the introduction of D11 describes that peptides represent an attractive strategy for the manipulation of unwanted immune responses to food proteins. In this context, D11 refers to a publication addressing tolerance to milk proteins following oral administration of partially hydrolysed milk proteins. The publication is D3 in these proceedings.

2.3.3 In summary, D11 discloses that a hydrolysed egg protein, namely ovalbumin, induces oral tolerance to native ovalbumin. The fact that the disclosure of D11 goes beyond that - it even identifies a specific peptide which suppresses ovalbumin-specific IgE responses - does not render D11 less relevant. On the contrary, D11 shows that the principle of providing a hydrolysed protein for inducing oral tolerance works also for egg protein ovalbumin, a major allergen of hen egg white.

2.4 The distinguishing features are that in claim 1 the use involves enzymatically hydrolysed egg proteins with a degree of hydrolysis between 15 and 28%.

This is not in dispute.

2.5 The problem stated in the patent (paragraph [0001]) is to induce oral tolerance to intact egg proteins in mammals likely to be allergic to eggs.

2.5.1 There is no reason to believe that the subject-matter of claim 1 would not solve this problem.

2.5.2 Therefore, the technical problem set out in the patent need not be reformulated.

2.6 Obviousness

2.6.1 The respondent argued that the skilled person starting from D11 would not have considered D3 because it was from a remote technical field and did not belong to a neighbouring technical field. On this aspect, both parties referred to Case Law of the Boards of Appeal of the EPO, 9th edition, 2019 (Chapter I.D.8.2, first paragraph).

2.6.2 Before turning to neighbouring fields, the skilled person would have considered the state of the art in the specific technical field in question and, in particular, would have studied the closest prior art's disclosure. In the case at hand, the authors of D11 themselves place the publication's disclosure in the context of peptides and protein hydrolysates as tools for the induction of tolerance. It is in this context that D11 explicitly refers to the results discussed in D3.

2.6.3 Therefore, the question of how remote the disclosure of D3 is to the technical field of D11 does not arise. D11 refers to a method applicable across several technical fields to induce tolerance, namely by using peptides, and also points to the disclosure of D3. The skilled person reading the closest prior art would have been directly made aware of D3 and its teaching on induction of oral tolerance. Consequently, they would have turned to D3.

2.6.4 D3 discloses the following.

In its abstract, it is stated that:

- the purpose of the study is to determine whether oral tolerance can be induced with protein peptides
- partially hydrolysed and extensively hydrolysed cow's milk formulas are compared for their capacity to induce tolerance
- in conclusion, partially hydrolysed proteins are able to induce oral tolerance whereas extensively hydrolysed proteins are not

In the study's experiments, the partially hydrolysed formula used is an enzymatically (trypsin) hydrolysed whey formula (hydrolysis 18%), and the extensively hydrolysed formula is based on a pancreatic hydrolysate of isolated whey proteins (hydrolysis 28%). Whey proteins comprise the protein β-lactoglobulin, a potent allergen of cow's milk. The overall conclusion in D3 is that partially hydrolysed formulas are more suited than extensively hydrolysed formulas for actively inducing oral tolerance to cow's milk proteins.

2.6.5 The respondent argued that the skilled person would have refrained from applying a teaching valid for milk protein to egg proteins because the proteins were different. In its view, induction of oral tolerance using a partially hydrolysed whey-based formula prevented the immune system from developing allergic reaction to whey proteins but not to egg proteins.

However, the skilled person would know that allergenic and tolerogenic peptides are specific to the protein. Contrary to what the respondent appears to suggest, the skilled person would not have expected that partially hydrolysed whey-based formula induces oral tolerance to egg proteins. But they would have been aware of the immunological mechanism behind allergy and induction of tolerance. As the appellant pointed out, induction of oral tolerance involves low dose antigen exposure that favours the induction of regulatory T cells. In view of the immunological mechanisms involved, the skilled person would not have restricted themselves solely to the knowledge on egg proteins.

2.6.6 Consequently, the skilled person would have applied the knowledge from D3 (i.e. to enzymatically hydrolyse proteins to obtain partially hydrolysed proteins) to

induce oral tolerance. With regard to the teaching in both D11 and D3, the skilled person would have expected this to solve the technical problem.

2.6.7 As to the degree of hydrolysis, D3 instructs the skilled person to use partially hydrolysed proteins. The degree of hydrolysis exemplified is of 18%. The skilled person would have been aware that this specific value relates to whey proteins which have been hydrolysed enzymatically with trypsin. Nevertheless, this value would have provided the skilled person with a starting point as to what partially hydrolysed means. This value is fully within the range for the degree of hydrolysis called for in claim 1.

2.6.8 Furthermore, as the respondent itself pointed out, reduced allergenicity is a prerequisite for any agent to be used for inducing oral tolerance. While extensively hydrolysed proteins have low allergenic potential (e.g. D3, page 268, right column; patent in suit, paragraph [0006]), they do not induce oral tolerance, as D3 teaches. The skilled person would therefore have provided an enzymatically produced partial hydrolysate of egg proteins with a degree of hydrolysis high enough to have reduced allergenicity and low enough to induce oral tolerance.

2.6.9 Therefore, the board cannot agree with the opposition division that the skilled person would not have been led to the current invention, in particular to the sufficiently low residual allergenicity and sufficiently high capacity to induce oral tolerance at the degree of hydrolysis called for in claim 1.

2.7 To conclude, the subject-matter of claim 1 of the main request does not involve an inventive step (Article 56 EPC).

3. *Auxiliary requests - admission and order of requests*

As will be shown below, none of the auxiliary requests is allowable. Therefore, it is not necessary to assess whether these requests are to be admitted into the proceedings. Likewise, the specific order in which the respondent requested that the auxiliary requests be dealt with is immaterial for the present decision.

4. *Auxiliary requests AR 1A to 1C and 2*

4.1 In auxiliary requests AR 1A to 1C and 2, the degree of hydrolysis is restricted, compared to that of claim 1 of the main request (wording, see point VII). All these requests encompass a value for the degree of hydrolysis of 23%.

4.2 The respondent did not argue that additional technical effects occur in the more restricted value ranges called for in the auxiliary request. The respondent's argument was that arriving at a degree of hydrolysis within the more restricted value ranges would have been even less obvious to the skilled person.

4.3 Therefore, no rephrasing of the technical problem is required.

4.4 As explained above (see point 2.6.8), extensively hydrolysed proteins have low allergenic potential, but they do not induce oral tolerance. The skilled person would have worked in a range that provides partially hydrolysed proteins with a degree of hydrolysis high

enough to reduce allergenicity and low enough to induce oral tolerance. Contrary to what the respondent argued, the skilled person would have had a motivation to work above a degree of hydrolysis of 18%. It is not convincing that the skilled person - when applying the teaching of D3 and carrying out corresponding experiments - would only have adopted the specific value disclosed in D3, i.e. 18%, and have stopped the partial hydrolysation of proteins at a degree of hydrolysis of below 20 or 23%.

4.5 The respondent, referring to paragraph 5.6.4 of T 230/07, argued that when a prior art document disclosed ranges or values close to the claimed ones, this did not render obvious how to proceed to arrive at the claimed subject-matter.

4.5.1 In the case underlying the cited decision, the technical problem was to provide an alternative method of preparing a stable colloidal silicate binder dispersion. The closest prior art (D13) referred to an intermediate product (a specified solution) to which ammonia or ammonium hydroxide was added to form a gel. The competent board considered with regard to intermediate silicate solution of D13 that "there is however no time left in the process of D13 for the further steps defined in claim 1 at issue" (Reasons for the decision, point 4.5.2). Under these circumstances, where the process disclosed gives no room for carrying out further steps, the competent board concluded that there was no indication how the skilled person would have to proceed in order to arrive at a colloidal silicate dispersion.

4.5.2 In the case at hand, the situation is different. D3 presents a teaching to the skilled person, namely to

provide partially hydrolysed proteins - not extensively hydrolysed proteins - and exemplifies values for the degree of hydrolysis. Therefore, the skilled person would have found instruction on how to proceed to solve the technical problem.

4.6 Thus, none of auxiliary requests AR 1A to 1C and 2 involves an inventive step (Article 56 EPC).

5. *Auxiliary requests AR 9A to 9E*

5.1 In claim 1 of these request (wording, see point VII), the feature two stage enzymatic hydrolysis has been added. This feature is not in the claims as granted and is disclosed on page 5, lines 10 and 11, of the application as filed. The amendment is based on the description and may be examined under Article 84 EPC (G 3/14).

5.2 Article 84 EPC sets out: "The claims shall define the matter for which protection is sought. They shall be clear and concise and be supported by the description."

5.3 The feature added to claim 1 is a process feature. Claim 1 is not directed to a production process. Instead, it concerns a second medical use of a composition. The respondent has not explained what is the impact of the added feature on the matter for which protection is sought. Possibly, the added feature aims at further characterising or restricting the composition (or the enzymatically hydrolysed egg proteins) of claim 1.

5.4 However, the feature added to claim 1 blurs the matter for which protection is sought. First, it is not specified what kind of steps the two stage enzymatic

hydrolysis involves. Second, and more important, it is not clear if, and then by how far, the added feature restricts the subject-matter of claim 1 as granted, in particular the composition (or the enzymatically hydrolysed egg proteins) referred to in claim 1.

5.5 The board concurs here with decision T 1661/16 (Reasons for the decision, point 1.4.4): "The meaning, in terms of the limiting effect, of features introduced into a claim must be clear in order that the claim as a whole is clear. To argue ... that it is not relevant whether a limitation might or might not be present, does not overcome such objection, it simply emphasises ... that the claim is not clear."

5.6 Therefore, claim 1 as amended fails to clearly define the matter for which protection is sought. None of auxiliary requests AR 9A to 9E fulfils the requirements of Article 84 EPC.

6. *Auxiliary requests AR 4A and 7A to 7D*

6.1 The amendment in claim 1 of auxiliary requests AR 4A and 7A to 7D (wording, see point IX) is based on page 5, lines 10 to 21, of the application as filed.

6.2 In the application as filed, the step of raising the temperature to between 85°C and 95°C and holding it there for about up to 30 minutes is disclosed only in combination with "to inactivate the enzymes and terminate the hydrolysis" (application as filed, page 5, line 21). The amendment in claim 1 adds subject-matter because the inactivation of enzymes, which is disclosed as a mandatory result of the process, is no longer required. Moreover, inactivation of the enzymes is also not obtained implicitly because

claim 1 also encompasses situations where the heating step is carried out for too short a period.

Thus, the amendment in claim 1 encompasses added subject-matter.

6.3 To conclude, auxiliary requests AR 4A and 7A to 7D are not allowable because they do not fulfil the requirement of Article 123(2).

7. *Auxiliary requests AR 3, 6A to 6D*

7.1 In claim 1 of auxiliary requests AR 3 and 6A to 6D (wording, see point VII), it is specified that egg proteins have been hydrolysed using the bacterial serine endoprotease subtilisin.

7.2 In the application as filed, the only disclosure of subtilisin is found in a sentence on page 5, lines 13 to 15, which reads:

"A protease such as the bacterial serine endoprotease subtilisin (sold for example under the trade mark Alcalase®) is added and the mixture is maintained at about 55°C for at least two hours to effect a partial hydrolysis."

7.3 The respondent argued that according to the application as filed (page 5, lines 9 to 10), the egg proteins may be enzymatically hydrolysed by any suitable process known in the art. Therefore, the skilled person would have understood that the bacterial serine endoprotease subtilisin is disclosed in this passage as an example of a protease.

7.4 This is not convincing. The sentence in which the bacterial serine endoprotease subtilisin is disclosed belongs to a defined process according to which any of the proteases used (including the bacterial serine endoprotease subtilisin) is added to a specified mixture (the mixture), at a specified temperature and for a specified duration. Therefore, there is no direct and unambiguous disclosure of the feature added to claim 1 without the specified process conditions in the application as filed.

7.5 Thus, auxiliary requests AR 3 and 6A to 6D include added subject-matter (Article 123(2) EPC).

8. *Auxiliary requests AR 5A and 8A to 8D*

8.1 Claim 1 of auxiliary requests AR 5A and 8A to 8D (wording, see point VII) is based on claim 1 of auxiliary request AR 4A, but the protease is defined to be the bacterial serine endoprotease subtilisin.

8.2 The objection of added subject-matter set out above with respect to auxiliary request AR 4A and 7A to 7D applies also for these requests. The respondent did not provide any further comment with respect to these requests.

8.3 To conclude, auxiliary requests AR 5A and 8A to 8D are not allowable because they do not fulfil the requirement of Article 123(2) EPC.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.
2. The patent is revoked.

The Registrar: The Chairman:

A. Nielsen-Hannerup A. Haderlein

Decision electronically authenticated