DECISION
of 10 December 2002

Case Number: T 0944/99 - 3.3.8
Application Number: 89304034.5
Publication Number: 0340948
IPC: C12N 15/32
Language of the proceedings: EN

Title of invention:
Novel hybrid pesticidal toxins

Patentee:
MYCOGEN CORPORATION

Opponent:
SYNGENTA PARTICIPATIONS AG

Headword:
Pesticidal toxins/MYCOGEN CORPORATION

Relevant legal provisions:
EPC Art. 123(2)(3), 84, 83, 54, 56

Keyword:
"Admissibility of disclaimer - main request - no accidental
disclosure - (no)"
"Clarity - first and second auxiliary requests - (no)"
"Novelty - third auxiliary request - (yes)"
"Inventive step - third auxiliary request - (yes)"
"Sufficiency of disclosure - third auxiliary request - (yes)"

Decisions cited:
G 0004/92, G 0004/93, T 0597/92, T 0426/94, T 0917/94,
T 0596/96, T 0608/96, T 0863/96, T 0019/90
Case Number: T 0944/99 - 3.3.8

DECISION of the Technical Board of Appeal 3.3.8 of 10 December 2002

Appellant: Syngenta Participations AG
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Decision under appeal: Interlocutory decision of the Opposition Division of the European Patent Office posted 3 August 1999 concerning maintenance of European patent No. 0 340 948 in amended form.

Composition of the Board:
Chairman: L. Galligani
Members: F. L. Davison-Brunel
V. Di Cerbo
Summary and facts and submission

I. The appeal lies from the interlocutory decision of the Opposition Division to maintain in amended form the European patent No. 0 340 948 with the title "Novel hybrid pesticidal toxins" which was granted with thirty claims for all Designated Contracting States except ES (non-ES States) and with 25 claims for ES.

Granted claims 1 and 18 (non-ES States) read as follows:

"1. A hybrid non-naturally-occurring pesticidal protein toxin comprising a cytotoxic agent and a pest gut epithelial cell-recognition portion of a protein."

"18. A microorganism capable of expressing a toxin having the amino-acid sequence shown in Table 4."

II. The patent had been opposed under Article 100(a) EPC for lack of novelty and inventive step and under Article 100(b) EPC for insufficiency of disclosure. The Opposition Division decided that the amended claim request filed at oral proceedings fulfilled the requirements of Article 123(2)(3) EPC and Article 84 EPC and that the claimed subject-matter was novel over the teachings of document (1) and inventive over the combined teachings of documents (1) and (2) (see Section XII below). Sufficiency of disclosure was also acknowledged.

Claims 1 to 3 and 18 of the request accepted by the Opposition Division for the non-ES States read as follows:
"1. A hybrid non-naturally-occurring pesticidal protein toxin comprising a cytotoxic agent and a pest gut epithelial cell-recognition portion of a protein, provided that the cytotoxic agent and the cell-recognition portion are not both of *Bacillus* proteins."

"2. A toxin according to claim 1, wherein the cytotoxic agent is a ribosome-inactivating enzyme obtainable from a seed of barley, rye, corn or wild bean."

"3. A toxin according to claim 1, wherein the cytotoxic agent is a ribosome-inactivating enzyme selected from ricin, dianthin, saporin, gelonin, tritin, abrin and modecin."

"18. A microorganism transformed to express a toxin having the amino-acid sequence shown in Table 4."

Dependent claims 4 to 13 related to further features of the toxin of claim 1. Claims 14 to 16 were directed to DNAs encoding specific toxins. Claims 17 and 19 to 24 were respectively directed to a recombinant vector comprising said DNAs and to microorganisms transformed to express the specific toxins. Claims 25 and 26 related to intact cells of a unicellular microorganism containing the toxin. Claims 27 to 30 were directed to methods for controlling insects.

These claims differed from the granted claims only in respect of the disclaimer at the end of claim 1 and the slightly different formulation of claim 18.

The corresponding claims were accepted for ES.
III. The Appellants (Opponents) filed an appeal, submitted the statement of grounds of appeal and paid the appeal fee.

IV. The Respondents (Patentees) answered to the grounds of appeal.

V. Summons to oral proceedings were dispatched on 17 May 2002.

VI. With their letter dated 30 October 2002, the Appellants informed the Board that they would not attend oral proceedings.

VII. On 8 November 2002, the Respondents filed a further submission together with 12 auxiliary requests.

Claim 1 of auxiliary request 1 read as follows:

"1. A hybrid non-naturally-occurring pesticidal protein toxin comprising a cytotoxic agent and a pest gut epithelial cell-recognition portion of a protein, wherein the cell-recognition portion is of a *Bacillus thuringiensis* or a baculovirus protein, and the cytotoxic agent is of a different genus."

Claim 1 of auxiliary request 2 read as follows:

"1. A hybrid non-naturally-occurring pesticidal protein toxin comprising a cytotoxic agent and a pest gut epithelial cell-recognition portion of a protein, wherein the cell-recognition portion is of a *Bacillus thuringiensis* protein or a NPV fusogenic protein, and the cytotoxic agent is of a different genus."
Furthermore, in case the Board was minded to refuse the main request because of the disclaimer in claim 1, the Respondents requested that a question be sent to the Enlarged Board of Appeal on the issue of the allowability of a disclaimer under Article 123(2) EPC.

VIII. In a further submission, the Respondents requested that the oral proceedings be postponed until such time as the question relating to the allowability of disclaimers which was to be sent to the Enlarged Board of Appeal by another Board was settled.

IX. The Board informed the parties that oral proceedings were not postponed.

X. The Appellants sent further comments regarding the formal allowability of some of the auxiliary claim requests.

XI. At oral proceedings which took place on 10 December 2002, the Respondents withdrew the third auxiliary request filed on 8 November 2002 and replaced it with an amended third auxiliary request (deletion of claims 2 and 3). Claim 1 of this request was identical to claim 1 of auxiliary request 3 filed on 8 November 2002 and read as follows:

"1. A hybrid non-naturally-occurring pesticidal protein toxin comprising a cytotoxic agent and a pest gut epithelial cell-recognition portion of a protein, wherein the cell-recognition portion is of a Bacillus thuringiensis protein, and the cytotoxic agent is of a different genus."

All other claims were the same as the corresponding
claims of the request accepted by the Opposition Division except for the deletion of claims 2 and 3.

Corresponding amended claims for ES were also filed together with amended description pages 3, 4 and 22.

XII. The documents mentioned in the present decision are the following:


(2): WO 83/ 03 971


XIII. The arguments in writing by the Appellants insofar as they are relevant to the present decision may be summarized as follows:

Main request
Allowability of the disclaimer

There was no need of a disclaimer in the patent in suit as the pest gut epithelial cell-recognition portion could be characterized as part of a B.thuringiensis protein and the cytotoxic agent as one inhibiting protein biosynthesis.

Article 56 EPC, inventive step

- The closest prior art was document (1) which disclosed a process for altering the host range of B.thuringiensis toxins, this process comprising the in vitro recombination of the variable regions of two delta endotoxins genes and the expression
of the chimeric gene so obtained for the production of a hybrid toxin. Document (1) expanded this teaching to any toxin produced by a microbe.

- Starting from document (1), the technical problem underlying the alleged invention was to produce hybrid toxins wherein the cytotoxic agent and the cell-recognition portion were not both of Bacillus.

- The teaching of document (1) on its own made it obvious to prepare such hybrid toxins, all the more so that document (1) made clear which portion of the B.thuringiensis toxin was the cell-recognition portion.

Furthermore, the use of diphtheria toxin was rendered obvious by the combination of the teachings of documents (1) and (2), which latter document disclosed the use of hybrid molecules comprising the diphtheria toxin linked to a polypeptide ligand capable of selectively recognizing a predetermined class of cells for the treatment of human disorders. The person skilled in the art would have interpreted the technical teaching of document (2) as being also applicable to plant cells, as diphtheria toxin was known as a potent inhibitor of plant protein synthesis.

**Article 83 EPC, sufficiency of disclosure**

The cytotoxic agents which were cited as useful to introduce in the hybrid toxin of claim 1 were ribosome inactivators from plants and their effects on plants was known to be unpredictable. Accordingly, there were
doubts as to whether they would be effective as part of the chimeric toxin.

**Auxiliary requests 1 to 3 filed on 8 November 2002**

**Article 84 EPC, clarity**

The use in claim 1 of these requests of the phrase "..is of a different genus" was unclear as the term genus was not an art-recognized term to distinguish a protein (the cytotoxic agent) from another protein (the baculovirus or the NPV protein).

**Auxiliary request 3 filed on 8 November 2002**

**Article 54 EPC, novelty**

Claim 1 where the disclaimer was replaced by positive features defining the pest gut epithelial cell-recognition portion and the cytotoxic agent was anticipated by the teaching of document (1) that the pesticide encoded by the DNA sequence used as a starting material for the invention process can be any toxin produced by a microbe. It was also anticipated by the teaching of document (6) which disclosed fusion proteins similar to the one disclosed in Example 1 of the patent in suit.

**XIV. The arguments by the Respondents in writing and during oral proceedings insofar as they are relevant to the present decision may be summarized as follows:**

**Main request**

**Allowability of the disclaimer**

The disclaimer was inserted in claim 1 at the opposition stage in order to impart novelty over the
teaching of document (1). In accordance with the case law, it was allowable to exclude an accidental novelty-destroying prior disclosure. Document (1) was such an accidental anticipation: it only disclosed modifying variable regions of B.thuringiensis endotoxin, did not describe how the modified toxin worked nor that it comprised two functionally different parts. Although the modifications brought to the toxin amounted to the isolation of a hybrid toxin, this toxin was conceptually quite different from the claimed hybrid toxin which comprised portions of proteins from another source than B.thuringiensis. Disclaiming the disclosure of document (1) was, thus, allowable. Should the Board see this otherwise, then the question of the allowability of the disclaimer under Article 123(2) EPC should be referred to the Enlarged Board of Appeal.

Article 83 EPC, sufficiency of disclosure

The patent in suit provided one example of how to produce a chimeric toxin as claimed in claim 1. At the priority date, it was a matter of common general knowledge to isolate genes. This was especially true for the genes which were necessary to carry out the present invention since the function of the proteins they encoded was known. The skilled person, thus, would have no difficulties in identifying them.

Article 54 EPC, novelty

None of the documents mentioned in the course of the proceedings including document (6) submitted at the opposition stage and refused by the Opposition Division for being late filed disclosed a hybrid toxin with the features mentioned in claim 1. The subject-matter of
the main claim request was novel.

Article 56 EPC; inventive step

- The closest prior art was document (1) which addressed the problem of obtaining variations in the host specificity of the *B.thuringiensis* toxins and taught to combine various portions of said toxins. In contrast, the present invention was concerned with varying the toxic agent to be targeted to insect cells by the cell-recognition portion of a *B.thuringiensis* toxin.

- This approach was not suggested in document (1). It was in fact a lateral step whereby one only kept one property of the *B.thuringiensis* toxin (the recognition of the target cells) but nonetheless retained the toxic activity by use of further means.

- It was only with hindsight that the skilled person would think of combining the teachings of documents (1) and (2). Indeed, document (1) made no mention of document (2), and this latter document was in the medical field whereas the earlier was concerned with an insect pathogen. Furthermore, document (2) did not deal with transferring different toxins to mammalian cells but with transferring one toxin (diphtheria toxin) to different kinds of mammalian cells with the help of a ligand specific for each kind.

For these reasons, inventive step had to be acknowledged.
Auxiliary requests 1, 2 and auxiliary request 3 as amended

The amendments brought into claim 1 were destined to further characterize the claimed subject-matter and were clear.

Auxiliary request 3 as amended

This request which did not contain claims 2 and 3 as maintained by the Opposition Division was filed at oral proceedings because the Board of appeal appeared to accept the Appellants' position that the requirement for sufficiency of disclosure was not fulfilled in relation to the hybrid toxins comprising a ribosome inhibitor other than diphtheria toxin. All that was said about the main claim request under Articles 83, 54 and 56 EPC equally applied to this request.

XV. The Appellants requested in writing that the decision under appeal be set aside and that the European patent No. 0 340 948 be revoked.

The Respondents requested that the appeal be dismissed or, alternatively, that the decision under appeal be set aside and the patent be maintained on the basis of auxiliary requests 1 or 2 filed with letter dated 8 November 2002, or auxiliary request 3 filed at oral proceedings (ie. claims 1 to 27 for all Designated Contracting States except ES and claims 1 to 22 for ES).

Reasons for the decision
Main request: claim request accepted by the Opposition
Division
Article 123(2) EPC; allowability of the disclaimer

1. The disclaimer in claim 1 excludes from the scope of protection hybrid non-naturally-occurring pesticidal protein toxins comprising a cytotoxic agent and a cell recognition-portion which are both of Bacillus proteins. It was inserted in claim 1 at the opposition stage in order to impart novelty to the claimed subject-matter over the teaching of document (1) and has no support in the application as filed.

2. According to the case law of the boards of appeal, it is possible in particular circumstances, such as in the case of an accidental anticipation of the invention, to introduce a disclaimer in a claim based on a well-defined accidentally novelty-destroying prior art document (cf. eg T 917/94 of 28 October 1999; T 596/96 of 14 December 1999; T 426/94 of 22 May 1996; T 608/96 of 11 July 2000). As explained eg in decision T 608/96 (cf. point 6 of the reasons), an "accidentally novelty-destroying disclosure" is a disclosure which the skilled person, confronted with the patent specification or its underlying technical problem, would not take into consideration because either it belongs to a completely different technical field or it cannot contribute anything to the solution of the underlying technical problem. This means that a novelty-destroying disclosure can be considered as accidental only when it is not at all relevant for the assessment of inventive step (cf. also T 863/96 of 4 February 1999). If such conditions are not met, the disclaimer is not allowed under Article 123(2) EPC.
3. Document (1) discloses a process for extending the pesticidal effects of *Bacillus* toxins past their natural host range. The process comprises linking the variable regions of two different *B. thuringiensis* toxin genes. This results in a DNA sequence encoding a hybrid toxin which has the toxic activity of one of the toxins and exerts this activity on the insects to which the other toxin is deleterious in nature. Thus, document (1), like the patent in suit, is in the field of agriculture, more specifically, in the field of microbial pesticides. It attempts to solve the technical problem of diversifying the means of killing a group of insects. This is also the technical problem which the patent in suit purports to solve. It is for this reason that document (1) was considered by all parties as the closest prior art to the invention, which is also the Board's opinion.

4. The Respondents' arguments in favour of the accidental nature of the anticipation by document (1) (see Section XIV, above) rely on the differences in concepts between the solutions provided in said document and in the patent in suit to the technical problem of diversifying the means of killing insects. While possibly relevant to inventive step, these arguments do not change the fact that, as above shown, document (1) does not fulfill any of the conditions required for it to be considered as an accidental disclosure.

5. Accordingly, it is concluded that document (1) is not an accidental anticipation of the claimed subject-matter and, thus, the disclaimer introduced in claim 1 renders the said claim (and, consequently, the main request) unallowable under Article 123(2) EPC.
6. The above finding is fully in line with the established case law on "disclaimers", namely that a disclaimer is admissible only for excluding from the ambit of a claim, for the purpose of restoring novelty, an "accidental disclosure" by a prior art document, said document not being relevant for the evaluation of inventive step (cf, T 863/96, T 596/96 and T 917/94 supra; T 597/92, OJ EPO 1996, 135). Under these circumstances, there is no need to refer a question to the Enlarged Board of Appeal.

**Auxiliary requests 1 and 2**

*Article 84 EPC; clarity of the claims*

7. In claim 1 of both these requests, the cytotoxic portion of the hybrid pesticidal toxin is characterized as being of a *genus* different from that of the cell recognition portion, this latter portion being itself defined as being of viral origin (baculovirus protein: auxiliary request 1; NPV fusogenic protein: auxiliary request 2). As the term *genus* is not an art-recognized term for the classification of viruses, this characterizing feature (and, therefore, claim 1 as a whole) is intrinsically unclear. Thus, auxiliary requests 1 and 2 do not fulfill the requirements of Article 84 EPC.

**Auxiliary request 3**

*Admissibility into the proceedings*

8. The request was filed during oral proceedings and differs from the request accepted by the Opposition Division (see Section II, above) in that claim 1 is worded in terms of positive features (see Section XI above) and claims 2 and 3 are deleted.
9. In the Board's judgment, the deletion of claims 2 and 3 is needed and appropriate to take into account the objection under Article 83 EPC in relation to ribosome inactivators. It does not put the Respondents in a more advantageous situation than they were before the Appellants appealed, no more than the amended version of claim 1 does as it is restricted in scope compared to claim 1 accepted by the Opposition Division. The Appellants cannot be taken by surprise since claim 1 was already part of the auxiliary request 3 filed on 8 November 2002, which they commented upon in writing and claims 2 and 3 were deleted in answer to their own submissions under Article 83 EPC (point 2.2.2 of the grounds of appeal) that there was insufficiency of disclosure in relation to ribosome inactivators other than diphtheria toxin. Otherwise stated, the auxiliary request does not offend the principles laid down in the Enlarged Board's decisions G 4/92 (OJ EPO 1994, 149) and G 4/93 (OJ EPO 1994, 875). Therefore, it is accepted in the proceedings in replacement of the auxiliary request 3 filed on 8 November 2002.

10. A basis for claim 1 is found in the application as filed on page 2, lines 32 to 34 (the cell-recognition portion) and page 3, lines 50 to 54 (mentioning a variety of enzymes which are not of Bacillus origin as the cytotoxic agent). The Board, furthermore, agrees with the Opposition Division that the amendment carried out in claim 18 at the opposition stage finds support both in claim 20 and on page 2, line 31 as originally filed. The scope of claim 1 has been reduced compared to that of granted claim 1 (see Section I, above) by specifying the origins of the two portions of the

*Articles 123(2)(3) and 84 EPC.*
The requirements of Article 123(2)(3) EPC are fulfilled.

11. The Appellants' objection for lack of clarity of claim 1 of auxiliary requests 1 and 2 for the reason given in point 7 above does not apply to claim 1 of auxiliary request 3 which does not mention the baculovirus or the NPV protein. Here, the cell-recognition portion is characterized as being of \textit{Bacillus thuringiensis} origin, \textit{Bacillus} being known in the art as a term used to identify a genus. Thus, the skilled person would have no difficulties in understanding the wording "and the cytotoxic agent is of a different genus" as meaning that this cytotoxic agent is not of \textit{Bacillus} origin, The requirements of Article 84 EPC are fulfilled.

\textit{Article 83 EPC; sufficiency of disclosure}

12. The Board notices that the patent in suit provides one example of how to construct a hybrid non-naturally-occurring pesticidal protein toxin as claimed in claim 1. Furthermore, instructions are given on pages 11 to 13 on how to isolate the chimeric toxin gene: microbial hosts, expression vectors and selection methods for the recombinant constructs are described. On pages 21 and 22, methods needed to determine the activity of the hybrid toxin are explained. In absence of any evidence that these instructions could not be successfully applied and taking into account that the priority date of the patent in suit is 28 April 1988, a time when genetic engineering techniques were all part of the common general knowledge (see the reference to the \textit{Molecular Cloning: A Laboratory Manual} on page 25 of the patent in suit), the Board decides that the...
The Appellants pointed out (point 2.2.2 of the grounds of appeal) that one could not be sure of the effect of the ribosome inactivators which are mentioned in the description as potential cytotoxic agents because the effect of these inactivators on plant cells was unpredictable. The Board fails to see the relevance of this observation to the present technical situation which requires that insects be killed. And, besides, in accordance with the case law (T 19/90, OJ EPO 1990, 474), it is only when doubts are substantiated by verifiable facts that they can be considered as potentially valid arguments against sufficiency of disclosure. No such facts have been put forward by the Appellants who bear the onus of proof.

The requirements of Article 83 EPC are, therefore, considered to be fulfilled.

Article 54 EPC, novelty

Claim 1 requires that in the hybrid toxin, the cell-recognition portion is of B.thuringiensis and the cytotoxic agent be of a different genus. These specific features are not disclosed in document (1) wherein the only reference to hybrid toxins other than those made from functionally undefined portions of Bacillus endotoxin genes reads (page 4, lines 9 and 10): "The pesticide encoded by the DNA sequence used as a starting material for the invention process can be any toxin produced by a microbe." As for document (6), it discloses hybrid toxins where the entire endotoxin is combined with other protein fragments (page 2, last
Thus, none of these documents affects novelty. The requirements of Article 54 EPC are fulfilled.

**Article 56 EPC; inventive step**

16. The closest prior art is document (1) which is concerned with diversifying the means for killing insects. It discloses that hybrid insecticidal toxins may be produced by recombination between the variable regions of the delta-endotoxin genes of two *Bacillus* species and subsequent expression of the chimeric constructs. The hybrid toxins have an expanded host range as may be seen in Chart A. It is stated on page 4: "The pesticide encoded by the DNA sequence used as starting material for the invention process can be any toxin produced by a microbe. For example, it can be a polypeptide which has toxic activity toward a eucaryotic multicellular pest, such as insects, e.g., coleoptera, ...; or arachnids; gastropods; or worms..."

17. Starting from the closest prior art, the problem to be solved can be defined as the provision of further means for killing insects.

18. The solution given in claim 1 is hybrid insecticidal toxins whereby the first part of the toxin is from *B.thuringiensis* and serves to recognize the insect cells whereas the second part is not from the genus *Bacillus* but, nonetheless, has cytotoxic properties towards insects.

19. Document (1) does not mention that there are separate domains in the variable regions of the delta-endotoxins and, a fortiori, it does not suggest that advantage
could be taken from this structural property to produce further active hybrid toxins where only one portion is of \textit{Bacillus} origin. In the Board's judgment, it cannot affect the inventive step of the claimed subject-matter on its own.

20. In this respect, the Board is not convinced by the Appellants' argument that the skilled person \textit{deducing} from Chart A that there must be two domains in the delta-endotoxins would find it obvious to use one of them independently from the other. Reading in this chart that it should not be necessary that both domains be of \textit{B.thuringiensis} to get an active toxin can only be done with the hindsight knowledge of the presently claimed subject-matter. In the same manner, the Board reads the passage of document (1) cited in point 16 above as giving information relating to the activity spectrum of the toxin and not as a suggestion making obvious a toxin such as claimed, comprising two parts, one only of them being of \textit{Bacillus} origin.

21. The Appellants also argued that the combination of the teachings of documents (1) and (2) rendered the claimed subject-matter obvious. Document (2) is in the field of medicine. It discloses targeting the diphtheria toxin to specific cells which need to be destroyed, by joining said toxin to a ligand which specifically recognizes these cells such as, for example, polypeptide hormones. For doing so, chimeric genes comprising the gene encoding the diphtheria toxin and the gene encoding the hormone are isolated and expressed.

22. Document (1) does not mention document (2) and document (2) does not suggest that the invention it
relates to, can be used in any other field than medicine. The Board is of the view that the field of microbial pesticides in agriculture and that of the treatment of human medical disorders are so far apart that it is once more only with hindsight that the teachings of documents belonging to one or the other would be combined by the person skilled in the art.

23. For these reasons, an inventive step is acknowledged.

24. The above conclusions are also valid for the claim request for ES.

25. Pages 3, 4 and 22 were amended to put the description into line with the invention as claimed in the patentable third auxiliary request. The amendments do not contain subject-matter which extends beyond the content of the application as filed. The requirements of Article 123(2) EPC are fulfilled.

Order

For these reasons it is decided that:

1. The decision under appeal is set aside.

2. The case is remitted to the first instance with the order to maintain the patent on the basis of the following documents:

   claims: auxiliary request 3 filed at the oral proceedings (ie claims 1 to 27 for all Designated States except ES and claims 1 to 22 for ES);
description: pages 3, 4 and 22 as filed at the oral proceedings; page 3a filed on 17 March 1998; pages 5 to 21 and 23 to 26 as granted;

drawings: as granted.

The Registrar: 

The Chairman:

A. Wolinski

L. Galligani