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**D E C I S I O N**  
**of 3 December 2002**

**Case Number:** T 1115/97 - 3.3.4

**Application Number:** 85101422.5

**Publication Number:** 0154204

**IPC:** C12N 15/01

**Language of the proceedings:** EN

**Title of invention:**  
Herbicide resistance in plants

**Patentee:**  
MGI PHARMA, INC.

**Opponent:**  
SYNGENTA PARTICIPATIONS AG  
E.I. Du Pont de Nemours & Company, Inc.

**Headword:**  
Herbicide resistant plant/MGI

**Relevant legal provisions:**  
EPC Art. 56

**Keyword:**  
"Inventive step - all requests - (no)"

**Decisions cited:**  
T 0737/96

**Catchword:**  
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Case Number: T 1115/97 - 3.3.4

**D E C I S I O N**  
**of the Technical Board of Appeal 3.3.4**  
**of 3 December 2002**

**Appellant:** MGI PHARMA, INC.  
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**Decision under appeal:** Decision of the Opposition Division of the  
European Patent Office posted 5 September 1997  
revoking European patent No. 0154204 pursuant  
to Article 102(1) EPC.

**Composition of the Board:**

**Chairman:** U. M. Kinkeldey  
**Members:** A. L. L. Marie  
S. C. Perryman

## Summary of Facts and Submissions

I. European Patent EP-0 154 204 was granted on the basis of 15 claims, claims 1, 6 and 11 of which read:

"1. A plant, the growth of which is resistant to inhibition by a 2-(2-imidazolin-2-yl)pyridine or -quinoline herbicide or by a sulfonamide herbicide, at levels which normally inhibit the growth of that plant, wherein said resistance is conferred by an altered acetohydroxyacid synthase resistant to inhibition by said herbicide at levels which normally inhibit the activity of an unaltered acetohydroxyacid synthase."

"6. A plant tissue culture, the growth of which is resistant to inhibition by a 2-(2-imidazolin-2-yl)pyridine or -quinoline herbicide or by a sulfonamide herbicide, at levels which normally inhibit the growth of said tissue culture, wherein said resistance is conferred by an altered acetohydroxyacid synthase resistant to inhibition by said herbicide at levels which normally inhibit the activity of an unaltered acetohydroxyacid synthase."

"11. A seed from which a plant can be grown, the growth of which plant is resistant to inhibition by a 2-(2-imidazolin-2-yl)pyridine or -quinoline herbicide or by a sulfonamide herbicide at levels which normally inhibit the growth of said species of plant, wherein said resistance is conferred by an altered acetohydroxyacid synthase resistant to inhibition by said herbicide at levels which normally inhibit the activity of an unaltered acetohydroxyacid synthase."

- II. The patent was opposed on the grounds of Article 110(a)(b)(c) EPC for lack of inventive step (Article 56 EPC), insufficiency of disclosure (Article 83 EPC) and extension of the subject-matter beyond the disclosure of the application as filed (Article 123(2) EPC). Article 53(b) EPC was also invoked.
- III. The patent was revoked pursuant to Article 102(1) EPC, because of non-compliance of the main, first and second auxiliary requests submitted during the oral proceedings before the opposition division with the requirements of Articles 53(b), 83 and 56 EPC, respectively.
- IV. The patentee filed an appeal against the decision of the opposition division.
- V. The Board issued on 22 April and 20 July 2002 two communications pursuant to Article 11(2) of the rules of procedure of the boards of appeal.
- VI. In reply to these communications, the appellant submitted on 15 November 2002 a new main and four auxiliary requests. The main request contained seven claims, claim 1 of which read:

"1. A monocotyledon plant, the growth of which is resistant to inhibition by a 2-(2-imidazolin-2-yl) - pyridine or -quinoline herbicide or by a sulfonamide herbicide at levels which normally inhibit the growth of the sensitive parental plant from which the resistant plant is derived, wherein said resistance is conferred by an altered acetohydroxyacid synthetase

resistant to inhibition by said herbicide at levels which normally inhibit the activity of the unaltered acetohydroxyacid synthetase of the sensitive parental plant from which the resistant plant is derived, and wherein said plant is capable of transmitting said resistance to progeny."

Claims 2 to 5 further characterized the plant of claim 1. Claims 6 and 7 were respectively directed to a plant tissue culture and a seed derived from the plant of claims 1 to 5.

The first auxiliary request contained six claims and only differed from the main request by the deletion of claim 5.

The second auxiliary request was identical to the first one, except for claim 1, in which "*obtainable by selection in tissue culture of spontaneous variants or direct mutants produced by a mutagenesis procedure,*" was inserted after "*A monocotyledon plant*".

The third auxiliary request contained six claims, identical to that of the first auxiliary request, except for claim 1 which read:

"1. A method for producing a monocotyledon plant the growth of which is resistant to inhibition by a 2-(2-imidazolin-2-yl) -pyridine or -quinoline herbicide or by a sulfonamide herbicide at levels which normally inhibit the growth of the sensitive parental plant from which the resistant plant is derived, wherein said resistance is conferred by an altered acetohydroxyacid synthetase resistant to inhibition by said herbicide at

levels which normally inhibit the activity of the unaltered acetohydroxyacid synthetase of the sensitive parental plant from which the resistant plant is derived, and wherein said plant is capable of transmitting said resistance to progen [sic], which process comprises use of selection in tissue culture of spontaneous variants or direct mutants or direct or indirect mutants produced by a mutagenesis procedure."

Further, claims 2 to 4 differed from the corresponding claims of the first auxiliary requests by the fact that they were formulated as method-claims.

The fourth auxiliary request was withdrawn at the onset of the oral proceedings, which were held on 3 December 2002.

VII. The following documents are mentioned in this decision:

- (1) B.G. Gengenbach et al., Proc. Natl. Acad. Sci. USA, 1977, Vol. 74, No. 11, pages 5113 to 5117
- (2) J.K. Bryan in "The Biochemistry of Plants", 1980, Vol. 5, pages 403 to 452
- (5) "Modes of Action of Herbicides", F.M. Ashton and A.S. Crafts editors, John Wiley and Sons Inc. ed., 1981, pages 131 to 133
- (6) K.A. Hibberd and C.E. Green, Proc. Natl. Acad. Sci. USA, 1982, Vol. 79, pages 559 to 563

- (7) C.P. Meredith and P.S. Carlson in "Herbicide Resistance in Plant Cell Culture", LeBaron et al. editors, 1982, pages 275 to 290
- (9) K. Hughes in "Handbook of Plant Cell Culture", Evans et al editors, 1983, pages 442 to 460
- (11) R.S. Chaleff, Science, 1983, Vol. 219, pages 676 to 682
- (12) J. Duesing, North Central Weed Control Conference, Columbus, Ohio, 1983, Vol. 38, pages 143 to 147
- (13) D.L. Shaner et al., Proc. Southern weed Society, 37th Annual meeting, 1984, page 364
- (14) N.S. Yadav and S.A. Bernard, 11th Aharon Katzir-Katchalski Conference, Jerusalem, Israel, Plant Molecular Biology, 1984, page D-11
- (15) T.B. Ray, Abstract of 1984 Meeting of the Weed Science Society of America, 1984, pages 87 to 88
- (16) K.S. Dumas and S.C. Falco, Abstracts of the 1984 Annual Meeting of the Weed Science Society of America, 1984, page 111, abstract H 121
- (17) R.A. LaRossa, Abstracts of the Annual Meeting of the American Society for Microbiology, 1984, page 116, abstract H 146
- (18) S.C. Falco and K.S. Dumas, Abstracts of the Annual Meeting of the American Society for Microbiology, 1984, page 116, abstract H 157

(30) Declaration of Dr R. Chaleff

(33) R.I.S. Bretell and E. Thomas, *Theor. Appl. Genet.*,  
1981, Vol. 58, pages 55-58

VIII. The arguments submitted by the appellant in writing or during the oral proceedings, as far as they relate to Article 56 EPC, may be summarized as follows:

- the acetohydroxyacid synthetase (AHAS) was identified for the first time in the patent in suit as the sole (or primary) site of action of the imidazolinone and sulfonamide herbicides in plants. The mechanisms of action of these herbicides and of the resistance to them were also elucidated for the first time in the patent in suit.
- this teaching enabled the skilled person to prepare a resistant plant by a single mutation event.
- such an information was not to be drawn from the prior art. Document (13) only taught that ARSENAL, an imidazolinone herbicide, caused a reduction in corn of the levels of valine, leucine and isoleucine, but was silent about AHAS and did not determine the sensibility of the various enzymes involved in this metabolic pathway to the herbicide. Document (15) indicated that chlorsulfon blocked the synthesis of valine and isoleucine in peas and identified AHAS as the site of action of this sulfonylurea herbicide. However,



the sensibility of the other enzymes involved in the metabolic pathway were not determined, so that it was not excluded that they also were involved in the blocking of the synthesis.

- furthermore, although documents (14) and (17) described the inhibition of the growth of *E. coli* and *S. typhimurium*, respectively, by interaction of sulfometuron methyl, a sulfonamide herbicide, with AHAS and documents (16) and (18) described AHAS as the primary target of sulfometuron methyl in yeast, document (5) showed that microorganisms and plants did not react in the same way to the herbicide Amitrole, so that, basically, an extrapolation of the results obtained with prokaryotes or yeast to plants was not possible.
  
- document (2) showed in Figures 4 and 5 that the metabolic pathway of valine, leucine and isoleucine contained four enzymes which were all potential sites of action for the imidazolinone and sulfonamide herbicides and document (12) described four different mechanisms by which a plant may become resistant to a given herbicide.
  
- even if he had known that AHAS was the site of action of the herbicides, the skilled person would not have been confident in isolating a useful mutant, since the mutation may also have interfered with the ability of AHAS to bind the substrate or with the allosteric control of the enzyme.

- the skilled person would have considered the tissue culture method disclosed in documents (1) and (6) as appropriate for isolating the resistant mutant plant of the patent in suit, only if the identity of the mechanisms of resistance leading to the resistant plants of documents (1) and (6) with that of the plants of the patent in suit had been proven. However, document (1) identified neither the mechanism of action of the natural T-toxin used nor the mechanism of resistance against it and the allosteric mechanisms of pathway inhibition as mediated by natural lysine and threonine used in excessive concentrations in document (6) was totally different from the toxic action of herbicides. Furthermore, document (6) did not show how resistance arose and document (1), by showing that the resistance to T-toxin was due to mitochondrial genes, casted doubts on the possibility to isolate mutants from nuclear genes, which were subjected in tissue culture method to less selection pressure than the extranuclear genes.
  
- according to document (30), a declaration by Dr Chaleff, the use of sub-lethal concentrations of herbicides as in the patent in suit was not expected to lead to success.
  
- document (33) showed that T-toxin-resistant plants were regenerated from control Tms-cultures which had been maintained for one year on agar medium without exposure to T-toxin and casted doubts on the value of the tissue culture method.

- since the tissue culture selection method of documents (1) and (6) did not provide a reasonable expectation of success, the skilled person was not in a "one-way-street" situation.
- no transmission of the resistance character to the progeny and no regeneration of the transformed monocotyledon plant was to be reasonably expected in view of document (7).

IX. The arguments presented by the respondents in view of Article 56 EPC may be summarized as follows:

- apart from the fact that document (15) defined AHAS as the "*primary site*" of action of the sulfonamide herbicides and used the same terminology as the patent in suit, the knowledge of whether AHAS was the sole site of action of the herbicides and of the mechanism of resistance to them was irrelevant, because the only way for isolating the desired mutant plant was to use the tissue culture method disclosed in documents (1) and (6), so that the skilled person was in a "one-way-street"-situation.
- it was therefore obvious for the skilled person to use the tissue culture method of documents (1) and (6) with the herbicides of documents (13) and (15) to isolate resistant plants with an altered AHAS.
- document (33) which showed that, after cultivation for one year in the absence of the T-toxin used in document (1), plants resistant to T-toxin were nevertheless isolated using the tissue culture

method, did not cast doubts on the value of this method, which did not cause the mutation, but only selected for the mutants.

- documents (1) and (7) showed the inheritability of the resistance to toxins in plants.

X. The appellant requested that the decision under appeal be set aside and that the patent be maintained on the basis of the main request or first, second or third auxiliary request all as submitted on 15 November 2002.

XI. The respondents (opponents) requested that the appeal be dismissed.

## **Reasons for the decision**

### *All requests*

#### *Articles 123(2)(3), 83 and 84 EPC*

1. In view of the findings on Article 56 EPC (see below), the Board does not see it as necessary to decide on the issues relating to these articles.

### *Main request*

#### *Article 56 EPC*

2. The Board agrees with the respondents and considers document (1) as the closest prior art. It describes the selection of cell lines resistant to *H. maydis* race T pathotoxin from *cms*-T maize callus( page 5114,

paragraph bridging the left and right columns), the regeneration of plants from these resistant cell lines (page 5115, paragraph bridging the left and right columns) and the expression (page 5114 to page 5115) and inheritance of toxin resistance in regenerated plants and their progeny (page 5113, right column, last sentence above heading "*Materials and Methods*" on page 5115, paragraph bridging the left and right columns). The resistant mutants are isolated using the tissue culture method, in which *cms*-T callus were grown for several selection cycles in the presence of progressively higher concentrations of T-toxin (abstract; page 5114, left column, paragraph "*Selection procedure*"; page 5114, right column, first paragraph). The resistance trait is cytoplasmically controlled (page 5116, right column first paragraph).

3. The technical problem to be solved that can be deduced from document (1) is the selection of plants resistant to other toxic molecules.
  
4. The solution as defined in claim 1 of the main request is the provision of monocotyledonous plants resistant to imidazolinone or sulfonamide herbicides known from document (13) and (15) to belong to the same family of herbicides characterized by their inhibitory action on the biosynthetic pathway leading to the amino acids valine, leucine and isoleucine using the tissue culture method defined in document (1) in presence of sub-lethal concentrations of these herbicides. The provision of the maize cell lines XA17, QJ22 and UV18 (example 7) shows that the problem has been solved in the patent in suit.

5. The relevant question in view of the assessment of inventive step of the subject-matter of the claims of the main request is whether the skilled person would have deduced this solution in an obvious manner from the cited prior art.
  
6. The skilled person in the context of the patent in suit can be defined as a (team of) scientist(s) involved in herbicide technology and plant biochemistry/physiology. This (team of) scientists is aware of the existence of the imidazolinone and sulfonamide family of herbicides disclosed in documents (13) or (15), because these documents are in its (their) technical area of interest. Further, it is motivated to produce useful plants resistant to these herbicides, because the advantage of having a herbicide at hand lies in the possibility to differentiate between a useful plant made resistant to this herbicide, the growth of which is favoured, and undesired weed depriving said plant of space and food to grow.
  
7. The value of the selection method of document (1) is confirmed by document (6) which describes the isolation of maize cell lines resistant to high concentration of lysine and threonine by cultivation of parental sensitive cells in presence of toxic, high concentrations of these amino acids. This trait, which is coded by a nuclear gene, is expressed and transmitted to the progeny (page 562, left column, first paragraph under heading "*Discussion*").
  
8. Its general applicability is highlighted by document (7), dealing with the appearance of herbicide resistance in plant cell cultures, which described it

as being a "*classical microbial mutant selection procedure*" and consisting in "*subjecting cell populations to drug-containing culture medium*" and mentions its application in the isolation of drug-tolerant plant mutants from tobacco, carrot and *Datura innoxia* (page 276, paragraphs 2 to 5; Table 14.1).

9. The Board is convinced that the use of the tissue culture method of document (1) was thus an obvious choice for the skilled person at the priority date of the patent in suit seeking to prepare mutants resistant to the sulfonamide and imidazolinone herbicides of documents (13) or (15). This method leads, due to its mode of action, to the isolation of **all** the (induced or spontaneous) mutants exhibiting the resistant phenotype, whether or not AHAS is the sole site of action of the herbicides. In this context, it is irrelevant whether there are possibly several mechanisms of resistance or several enzymes involved, as suggested by documents (12) and (2), respectively.
10. The Board, in contrast to document (30), a declaration by Dr Chaleff, considers that the successful use of sub-lethal concentrations of herbicide as selection agent in the tissue culture method, as disclosed in the patent in suit, is not surprising, since such sub-lethal concentrations of the selection agent have already been successfully used in document (1)(abstract, lines 6 to 10).
11. Document (33), analysing the plants regenerated from the maize tissue cultures of document (1), shows that plants resistant to T-toxin have been regenerated from unselected cultures which had been maintained for more

than one year on agar medium without exposure to the toxin (page 57). This teaching, in the Board's view, does not cast doubts on the suitability of the tissue culture method to select mutants, since this method is not a mutagenesis method and hence does not cause mutations, but only select for them. Such an appearance of spontaneous mutants is no surprise for the skilled person, since genetic variability arising spontaneously in plant cell cultures is described in document (11) on pages 677 to 678 (heading "*Genetic variability in cell cultures*"). In the Board's view, the teaching of document (33) would even strengthen the confidence of the skilled person in the suitability of the tissue culture method for isolating resistant mutants, since it shows that the success of said method does not depend on the way the resistance has occurred.

12. As far as the question of reasonable expectation of success, as raised by the appellant, is concerned, the present situation seems to be analogous to that described in decision T 737/96 (9 March 2000), in which the concerned Board had to decide on the expectation of success of the skilled person in relation to a generally known random phenomenon, such as mutagenesis. The Board came to the conclusion that it is not appropriate to attempt to evaluate the expectation of success in the context of such an unpredictable method, since the skilled person would adopt in such a situation a "*try-and-see*"-attitude. The analogy with the present case lies in the fact that the tissue culture method used in the patent in suit is also based on the appearance of (spontaneous or induced) mutations, ie the same unpredictable method as in decision T 737/96.



13. In this context, the possibility of failure of the transmission of the resistance trait to the progeny and of the regeneration of the resistant plant does not prevent these being an expectation of success by the skilled person. Certainty of success is not a requirement, so it is irrelevant that certainty will not exist using a random phenomenon such as mutagenesis. It can be noted that, although document (11) indicates that not all the traits expressed by the cultured cell are expressed by the whole plant (page 680, first column, second full paragraph), and at every developmental stage, document (9) reports an occasional failure to express the transmitted trait in the regenerated plant (page 446, lines 16 to 36) and document (7)(page 276, lines 28 and 29) teaches that the selected trait may not necessarily carry over to the regenerated plant, nevertheless none of these documents described a total failure of the transmission of the trait to the progeny or of the regeneration. Furthermore, document (11) states on page 676 (sentence bridging the first and second columns) that the regeneration of plants from cultured tissues has been achieved in the late 1950's and document (7) indicates on page 276 (lines 30 to 36), referring to the teaching of document (1), that regeneration and transmission to the progeny have been achieved. A similar teaching can also be found in document (6) (abstract, lines 3 to 6; page 562, first sentence under heading "*Discussion*" and page 563, left column, first full paragraph). The transmission of the selected trait to the progeny and the regeneration from mutated plant cell cultures do not hence appear to have been considered as a source of

any problems by the skilled person at the priority date of the patent in suit.

14. Therefore, the Board is convinced that it was obvious for the skilled person to use the tissue culture method of document (1) to isolate monocotyledonous plants resistant to herbicides belonging to the family of the imidazolinone and sulfonamide herbicides as described in documents (13) and/or (15) and in doing so he/she would have obtained a plant falling within the scope of claim 1. Therefore, the claims of the main request do not fulfil the requirements of Article 56 EPC.

*Auxiliary requests I to III*

15. This conclusion also applies to the three auxiliary requests, since claim 1 of the first auxiliary request is identical to claim 1 of the main request and the introduction of a reference to the tissue culture method in the product-claim 1 of the second and in the process-claim 1 of the third auxiliary requests cannot contribute to the inventive step in the light of the reasons given above showing that this method is the obvious choice for the skilled person.

**Order**

**For these reasons it is decided that**

The appeal is dismissed.

The Registrar

The Chairwoman

P. Cremona

U. Kinkeldey