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**Datasheet for the decision
of 1 July 2011**

Case Number: T 0324/10 - 3.3.09

Application Number: 03796844.3

Publication Number: 1594365

IPC: A23K 1/16

Language of the proceedings: EN

Title of invention:

Derivatives of seleno-amino acids with improved
bioavailability and method for assuring adequate dietary
requirements of selenium for livestock

Patentee:

Zinpro Corporation

Opponent:

-

Headword:

-

Relevant legal provisions:

EPC Art. 54, 56, 84

Relevant legal provisions (EPC 1973):

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Keyword:

"Clarity: Main, auxiliary request 1 (no), auxiliary requests
2-5 (yes)"

"Novelty (yes)"

"Inventive step (no)"

Decisions cited:

-

Catchword:

-



Case Number: T 0324/10 - 3.3.09

D E C I S I O N
of the Technical Board of Appeal 3.3.09
of 1 July 2011

Appellant: Zinpro Corporation
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Representative: Tomkinson, Alexandra
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Decision under appeal: Decision of the Examining Division of the
European Patent Office posted 28 September 2009
refusing European patent application
No. 03796844.3 pursuant to Article 97(2) EPC.

Composition of the Board:

Chairman: R. Menapace
Members: W. Ehrenreich
M. O. Müller

Summary of Facts and Submissions

I. European patent application No. 03 796 844.3, filed on 10 December 2003 as international application PCT/US2003/039096 in the name of *Zinpro Corporation*, was refused by the examining division in a decision issued in writing on 28 September 2009.

II. The decision was based on claims 1 to 14 as published in document WO 2004/075654 A1. Independent claims 1 and 9 read as follows:

"1. Metal L-seleno-alpha amino acid 1:1 complex salt compounds".

"9. A method of assuring adequate dietary requirements of selenium for livestock, comprising: adding as a feed ration supplement, a small but selenium enhancing effective amount of a metal L-seleno-alpha amino acid 1:1 complex salt compound to the daily feed ration".

In its decision the examining division cited documents D1 to D15, of which the following are relevant for the decision of the board:

- D1 G.N. Schrauzer "*Nutritional Selenium Supplement: Product Types, Quality, and Safety*" in: *Journal of the American College of Nutrition*, vol. 20, No. 1, 1-4 (2001);
- D2 G.N. Schrauzer "*Selenomethionine: A Review of its Nutritional Significance, Metabolism and Toxicity*" in: *The Journal of Nutrition*, vol. 130, No. 7, 1653-1656 (2000);
- D8 US-A 4 021 569;

- D12 H.A. Zainal et al. "*Potentiometric and spectroscopic study of selenomethionine complexes with copper(II) and zinc(II) ions*" in *Transition Metal Chemistry*, vol. 20, No. 3, 225-227 (1995).
- III. As to novelty the examining division concluded that D11 to D15 disclosed selenium-containing amino acid - metal complexes in which the ratio of amino acid/metal exceeded 1. Novelty was therefore acknowledged.
- IV. In assessing inventive step the examining division considered either D1 or D2 representative of the closest prior art, both describing the L-form of selenomethionine as an ingestible source of selenium. In the examining division's view the skilled person was incited to replace the amino acid methionine in the amino acid-methionine complexes described in one of the documents D3 to D10 by the L-selenomethionine according to D1 or D2 because it could expect that the resulting complexes would improve the bioavailability of selenium. Hence, inventive step of the claimed subject-matter was not acknowledged.
- V. A notice of appeal was filed by the applicant (hereinafter appellant) and the prescribed fee was paid on 25 November 2009. The statement of the grounds of appeal was received on 26 January 2010.

Enclosed with the grounds of appeal were two sets of claims for a new main and an auxiliary request (hereinafter auxiliary request 1). Claims 1 and 9 of the main request were identical to the corresponding claims underlying the decision under appeal (and to claims 1 and 9 of the patent application as originally

filed). In the auxiliary request 1, the L-seleno-alpha amino acid of claim 1 was restricted to L-seleno-methionine or Se-methyl-L-selenocysteine. Furthermore, claim 9 was renumbered to read claim 6 after deletion of preceding claims.

VI. In a communication dated 19 May 2011 the board gave its preliminary observations on the issues of clarity, novelty and inventive step.

As regards clarity it was stated that claim 9 of the main/claim 6 of the auxiliary request 1 were unclear because of the wording "*a small but selenium enhancing amount ...*".

Under point V of the communication dealing with inventive step the board set out that, as an alternative to the approach applied by the examining division of starting from D1 as closest prior art, a different approach could be to start from D12 as closest prior art and combine it with D2.

Furthermore, the board expressed its view that it was not credible that any metals other than those mentioned in claims 2 of the main/auxiliary request 1 (i.e. zinc, manganese, copper, cobalt, iron and chromium) were suitable as metal complex ions in selenoaminoacid complex salts for nutritional purposes.

VII. In response to this communication, the appellant, with its letter dated 15 June 2011, filed two further sets of claims as auxiliary requests 2 and 3. Claims 1 of both requests corresponded to claims 1 of the main and auxiliary request 1. Claim 9 of the auxiliary

requests 2 and claim 6 of the auxiliary request 3 corresponded to claim 9 of the main request and claim 6 of the auxiliary request 1, the subsequent dependent claims having been incorporated into these claims.

With the same letter the appellant communicated to the board that it would not attend the oral proceedings scheduled to take place on 1 July 2011 and requested that the appeal proceedings be continued in writing.

- VIII. In a notification dated 20 June 2011 the board informed the appellant that the date fixed for oral proceedings was maintained.
- IX. In a further communication sent by fax to the appellant on 28 June 2011 the board reminded the appellant that it had not dealt with the objection in point V of the previous communication and that the board maintained its position in this respect. It was left to the appellant to file amended claims in response.
- X. In reaction thereto the appellant, with a letter dated 29 June 2011, submitted sets of claims for auxiliary requests 4 and 5 in which the feature relating to the metal ions according to claim 2 had been incorporated into claim 1.
- XI. The appellant's arguments concerning inventive step provided in the grounds of appeal and in the letter dated 15 June 2011 can be summarised as follows:

(a) Starting from D1 as closest prior art:

L-selenoaminoacids as sources of selenium in vivo were known in the prior art, inter alia from D1. As was stated in the description of the application on page 9, lines 19 to 22, selenoaminoacids suffered from a low water solubility which affected bioavailability of selenium. Taking D1 as closest prior art, the claimed invention differed therefrom in that the L-selenoaminoacid (e.g. selenomethionine) was complexed with a metal ion to form a 1:1 complex. In comparison with selenomethionine alone the zinc 1:1 complex showed a better water solubility, an improved stability in solution and a better miscibility with food ingredients and, as a result, an increased bioavailability of selenium.

A skilled person faced with the problem of increasing the bioavailability of selenium, however, was not induced by D3 to D10 to complex L-selenomethionine with zinc, copper or an alternative metal, because these documents were concerned with increasing the bioavailability of trace elements like copper or zinc by complexing them with essential amino acids. Rather, D3 to D10 were said to lead the skilled person to a different solution, namely complexing an essential amino acid with the element selenium to increase the uptake of the latter.

In contrast to the essential amino acid methionine, L-selenomethionine and Se-methyl-L-selenocysteine were not essential amino acids and specific

mechanisms for their uptake did not exist. The skilled person reading D3 to D10 would therefore not consider replacing the essential amino acids like methionine with the non-essential amino acid L-selenomethionine. Although it was known from D3 to D10 that the bioavailability of metal in a metal- essential amino acid complex was improved, no prediction could be made as to whether the bioavailability of selenium from a metal-non-essential selenoaminoacid complex could be improved.

(b) Starting from D12 as closest prior art:

D12 was an academic study of the potentiometric and spectroscopic behaviour of solutions containing copper(II) and zinc(II)-ions and selenomethionine. It was presumed that complexes were formed between the metal ion and the seleno amino acid which, however, were neither isolated nor purified nor was their potential utility explored. In contrast, the applicant had prepared and isolated well-defined compounds and characterised them as 1:1 complexes of zinc and L-selenomethionine which were found to be suitable as a readily bioavailable source of selenium. D12 failed to recognise or teach the utility of the claimed complexes. A skilled person was therefore not motivated to use the claimed complexes as a source for selenium. D2 would not add any motivation to use the claimed complexes or the compounds of D12 in a nutritional way, since it dealt with completely different compounds.

XII. The appellant requested in writing that the appealed decision be set aside and that a patent be granted on the basis of the main request, alternatively on that of auxiliary request 1, both filed with the grounds of appeal dated 26 January 2010, or on the basis of auxiliary request 2 or 3, both filed with the letter dated 15 June 2011, or on the basis of auxiliary request 4 or 5, both filed with the letter dated 29 June 2011.

Reasons for the Decision

1. The appeal is admissible.

2. Clarity - Article 84 EPC

2.1 Main request: claim 9, Auxiliary request 1: claim 6

Both claims define a method for supplying livestock with suitable amounts of selenium via the 1:1 complex as claimed in claim 1 and contain the feature that the metal L-seleno-alpha amino acid 1:1 complex is added as a feed ration supplement "*in a small but selenium enhancing effective amount*".

When assessing the clarity of this feature one has to take into account the fact that, as is known to the person skilled in the art, the physiologically active amount of selenium strongly depends on the nature of the animal and the metabolism in its body. Therefore, the effective amount of selenium administered via the metal-L-selenoamino acid complex as a feed ration supplement is different for each animal. It follows

that in the absence of specific amount ranges of the complex depending on the nature, size and body weight of the respective animal, the amount in the feature in question remains undefined, so that it renders claim 9 of the main request and claim 6 of the auxiliary request 1 unclear, contrary to the requirements of Article 84 EPC.

As a consequence these two requests cannot be allowed.

2.2 Auxiliary requests 2 to 5

The above-mentioned deficiency under Article 84 EPC was removed by incorporating into the independent method claims the features of the subsequent dependent claims.

3. Novelty - Auxiliary requests 2 to 5

As 1:1 metal complexes of seleno-alpha amino acids in the enantiomeric L-form are not disclosed in any of the cited documents, the subject-matter of the invention as claimed is novel.

4. Inventive step - Auxiliary requests 2 to 5

4.1 Claims 1 of auxiliary requests 2 to 5 are all directed to 1:1 complexes of a metal with a L-seleno-alpha amino acid, the latter being restricted in auxiliary requests 3 and 5 to L-selenomethionine or Se-methyl-L-selenocysteine. In auxiliary requests 4 and 5 the metal ion is restricted to zinc, manganese, copper, cobalt, iron and chromium. Claims 1 of auxiliary requests 2 to 5 therefore all include as a specific embodiment the 1:1 complex of zinc with L-selenomethionine.

4.2 The subject-matter of the application

The claimed invention lies in the field of artificial food ingredients which are able to provide selenium to an animal body. The invention starts from the observation that the bioavailability of selenium from natural organic selenium sources, like selenium yeast in which selenium primarily exists in the form of L-selenomethionine-rich proteins, or from synthetic selenoaminoacids, is not optimal. Therefore, it was the objective of the invention to provide synthetic derivatives of seleno-amino acids with improved bioavailability (description, page 8, line 21 to page 9, line 22).

This objective is met by the provision of 1:1 complexes of a metal ion with an L-seleno-alpha amino acid and in a particularly preferred embodiment of the zinc L-selenomethionine 1:1 complex salt.

4.3 The closest prior art

The closest prior art can be represented either by D12 or by D1, as follows from what is set out below (points 4.3.1 and 4.3.2).

4.3.1 Starting from D12 as closest prior art

D12 discloses inter alia 1:1 complexes of selenomethionine with Zn^{2+} ions (page 225, left column "Summary" and "Experimental"). In Table 2 a complex of Zn^{2+} with racemic DL-selenomethionine is mentioned. Although D12 is mainly concerned with potentiometric

and spectroscopic studies of the complexes, it is expressly stated in the introductory part of this document (page 225, left column) that these studies were prompted inter alia by recent interest in selenomethionine-transition metal complexes in a nutritional role. This passage, together with the bibliographic reference [15] to the textbook "The Role of Selenium in Nutrition" made in D12 in this context, provides an unambiguous pointer to the use of selenomethionine-transition metal complexes as a selenium source in animal nutrition. It is known in the prior art and was stated by the applicant itself in the application (page 9, lines 12 to 22 of the description), that bioavailability of selenium is a critical aspect when administering synthetic selenium preparations to animals. It follows that - contrary to the appellant's contention (see page 3, last paragraph of its letter dated 15 June 2011) - the skilled person actually would have considered selenomethionine-transition metal complexes like those disclosed in D12 as a suitable selenium source.

The appellant's argument that in D12 the selenium complexes were not isolated, purified or characterised whereas, in the present application, the appellant had prepared and isolated well-defined compounds and characterised these compounds as the 1:1 zinc complexes of seleno-L-methionine is not convincing. The statement in the summary of D12 "Two new solids were prepared and identified by elemental microanalysis as $(SeMet)_2Cu$ and $(SeMet)_2Zn$ " [emphasis added by the board], i.e. as 2:1 complexes, implies that the corresponding 1:1 complexes, which were subjected to the same potentiometric studies (page 225, left column "Experimental") were already

known in solid form and analytically characterised and therefore available to the skilled person within the meaning of Article 54 EPC.

The claimed seleno-alpha amino acid 1:1 complexes differ from the 1:1 complexes of D12 only in that the selenomethionine in the complex is the enantiomeric L-form. As the experimental evidence provided in the application does not show any unexpected effect of the claimed 1:1 complex including the seleno amino acid in the enantiomeric L-form over the racemic DL form disclosed in D12, the problem to be solved is seen in providing an alternative metal 1:1 seleno amino acid complex as a nutritional supplement.

The use of the L-form of selenomethionine as a preferred form of selenium for supplemental use in human and animal nutrition was, however, already known from D2 (abstract and page 1655, left column). The skilled person was therefore incited to apply the L-form of selenomethionine also as a preferred alternative complex ligand instead of the DL-form disclosed in D12.

The use of the claimed metal L-selenoaminoacid 1:1 complex salt compounds, at least in the embodiment as zinc L-selenomethionine 1:1 complex, for the purpose in question was therefore obvious from a combination of D12 with D2.

4.3.2 Starting from D1 as closest prior art

D1 is concerned with nutritional selenium supplements and the importance of selenium for preventing diseases.

On page 1, left column it is stated in the section "Nutritional Forms of Selenium" that L-selenomethionine is the most appropriate supplement form of selenium because more than 80% of the total selenium in seleniferous corn is L-selenomethionine. It was further known to a skilled person that the bioavailability of the free selenoamino acids is reduced by their low solubility (see page 9, lines 12 to 15 of the description as originally filed). Therefore, there was a need to overcome the low bioavailability of these compounds.

The claimed subject-matter differs from the disclosure in D1 in that the L-selenomethionine is a complex ligand in a 1:1 complex with a metal ion, which is preferably zinc.

The experimental evidence in the application shows in Example 5 and Table 1 improvements in glutathione peroxidase activity of the Zn-L-Selenomethionine 1:1 complex over L-selenomethionine alone, due to its increased bioavailability.

Therefore, the problem to be solved is the provision of L-selenomethionine in a chemical form which improves its bioavailability.

Several documents cited as prior art in the application (page 9, lines 23 to 26) deal with 1:1 complexes of essential metal ions, like zinc, with amino acids, like methionine, which is the sulphur-homologue of selenomethionine.

In particular D8, stemming from the applicant itself, deals with 1:1 complexes of zinc with methionine. It is pointed out in column 1, lines 49 to 61 and in column 2, lines 6 to 20 that, in one aspect, the bioavailability of the essential element zinc and, in a further aspect, the bioavailability of the essential amino acid methionine are increased by ingesting the 1:1 zinc methionine complex. The skilled person would therefore conclude from D8 that, by reacting zinc ions with methionine to form a 1:1 complex, not only the bioavailability of the zinc ion - as alleged by the appellant in its grounds of appeal (points 11 to 14) - but also the bioavailability of the amino acid methionine would be improved.

D8 further points to the need for a ready solubility of the 1:1 complex by selecting a suitable anion (column 3, lines 28 to 33) and to the good stability of the complex which guarantees that "*the zinc and methionine can be readily utilized within an animal's body biochemical systems*" (column 4, lines 41 to 46). These particular properties of the 1:1 complex according to D8 exactly correspond to the properties attributed by the appellant to the claimed 1:1 zinc seleno-L-methionine complex in its letter dated 15 June 2011 (page 3, points a) and b)). Hence, a skilled person could expect that the bioavailability of the poorly soluble L-selenomethionine in its free form, as described in D1, could be improved by providing it in complex form as a ligand in a zinc 1:1 complex in analogy to D8.

That being so, the appellant's argument in point 19 of the grounds of appeal that it was not possible to

predict that the bioavailability of selenium from the non-essential amino acid would be improved when complexed with a metal is of no relevance.

5. For the reasons set out in points 4.3.1 and 4.3.2 above, the addition of a zinc-L-selenomethionine 1:1 complex as one embodiment of claims 1 of auxiliary requests 2 to 5 is not inventive in view of D12 in combination with D2 or of D1 in combination with D8. It follows that auxiliary requests 2 to 5 are not allowable either.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar

The Chairman

G. Röhn

R. Menapace