AQUEOUS CONCENTRATE AND PROCESS FOR PREPARING SAME

The aqueous trace element concentrate of the invention contains macro- and trace elements in ratios meeting the demands of human body and therefore it can excellently be used for the preparation of infusion solutions. It is characteristic of the compositions according to the invention that they contain xylitol. The compositions preferably comprise 0.01 to 1.5 mg of copper, 0.005 to 0.5 mg of selenium, 0.1 to 20.0 mg of zinc and 1.0 to 100 mg of magnesium in relation of 10 ml of concentrate. Furthermore, the invention relates to a process for preparing these trace element concentrates. This process comprises dissolving the macro- and trace elements as well as xylitol in water and then adjusting the pH value between 0.8 and 4.0.
### FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AT</td>
<td>Austria</td>
<td>GB</td>
<td>United Kingdom</td>
<td>MR</td>
<td>Mauritania</td>
</tr>
<tr>
<td>AU</td>
<td>Australia</td>
<td>GE</td>
<td>Georgia</td>
<td>MW</td>
<td>Malawi</td>
</tr>
<tr>
<td>BB</td>
<td>Barbados</td>
<td>GN</td>
<td>Guinea</td>
<td>NE</td>
<td>Niger</td>
</tr>
<tr>
<td>BE</td>
<td>Belgium</td>
<td>GR</td>
<td>Greece</td>
<td>NL</td>
<td>Netherlands</td>
</tr>
<tr>
<td>BF</td>
<td>Burkina Faso</td>
<td>HU</td>
<td>Hungary</td>
<td>NO</td>
<td>Norway</td>
</tr>
<tr>
<td>BG</td>
<td>Bulgaria</td>
<td>IE</td>
<td>Ireland</td>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>BJ</td>
<td>Benin</td>
<td>IT</td>
<td>Italy</td>
<td>PL</td>
<td>Poland</td>
</tr>
<tr>
<td>BR</td>
<td>Brazil</td>
<td>JP</td>
<td>Japan</td>
<td>PT</td>
<td>Portugal</td>
</tr>
<tr>
<td>BY</td>
<td>Belarus</td>
<td>KE</td>
<td>Kenya</td>
<td>RO</td>
<td>Romania</td>
</tr>
<tr>
<td>CA</td>
<td>Canada</td>
<td>KG</td>
<td>Kyrgyzstan</td>
<td>RU</td>
<td>Russian Federation</td>
</tr>
<tr>
<td>CF</td>
<td>Central African Republic</td>
<td>KP</td>
<td>Democratic People's Republic of Korea</td>
<td>SD</td>
<td>Sudan</td>
</tr>
<tr>
<td>CG</td>
<td>Congo</td>
<td>CI</td>
<td>Côte d'Ivoire</td>
<td>SE</td>
<td>Sweden</td>
</tr>
<tr>
<td>CH</td>
<td>Switzerland</td>
<td>CI</td>
<td>Côte d'Ivoire</td>
<td>SI</td>
<td>Slovenia</td>
</tr>
<tr>
<td>CI</td>
<td>Côte d'Ivoire</td>
<td>CZ</td>
<td>Czech Republic</td>
<td>SK</td>
<td>Slovakia</td>
</tr>
<tr>
<td>CM</td>
<td>Cameroon</td>
<td>DE</td>
<td>Germany</td>
<td>SN</td>
<td>Senegal</td>
</tr>
<tr>
<td>CN</td>
<td>China</td>
<td>DK</td>
<td>Denmark</td>
<td>TD</td>
<td>Chad</td>
</tr>
<tr>
<td>CS</td>
<td>Czechoslovakia</td>
<td>ES</td>
<td>Spain</td>
<td>TG</td>
<td>Togo</td>
</tr>
<tr>
<td>CZ</td>
<td>Czech Republic</td>
<td>FI</td>
<td>Finland</td>
<td>TJ</td>
<td>Tajikistan</td>
</tr>
<tr>
<td>DE</td>
<td>Germany</td>
<td>FR</td>
<td>France</td>
<td>TT</td>
<td>Trinidad and Tobago</td>
</tr>
<tr>
<td>DT</td>
<td>Denmark</td>
<td>GA</td>
<td>Gabon</td>
<td>UA</td>
<td>Ukraine</td>
</tr>
<tr>
<td>ES</td>
<td>Spain</td>
<td>GB</td>
<td>United Kingdom</td>
<td>US</td>
<td>United States of America</td>
</tr>
<tr>
<td>FI</td>
<td>Finland</td>
<td>GR</td>
<td>Greece</td>
<td>UZ</td>
<td>Uzbekistan</td>
</tr>
<tr>
<td>FR</td>
<td>France</td>
<td>HU</td>
<td>Hungary</td>
<td>VN</td>
<td>Viet Nam</td>
</tr>
</tbody>
</table>
AQUEOUS CONCENTRATE AND PROCESS FOR PREPARING SAME

The present invention relates to an aqueous concentrate of macro- and trace elements as well as to its preparation. The multicomponent aqueous concentrate of the invention containing macro- and trace elements is an injection particularly useful for the preparation of infusion compositions.

It is known that macro- and trace elements are indispensable constituents of nutritive solutions in the therapy of patients needing artificial nutrition (K. N. Jeejeebhoy: Clinical, Biochemical and Nutritional Aspects of Trace Elements, 1982, Alan R. Liss. Inc., New York, pp. 469 to 476). Practically, the supplementation with trace elements is chiefly assured by the trace element contaminations of amino acid solutions but this approach is not satisfactory; trace-element additives are employed for supplementing trace elements and preventing the occurrence of deficiency symptoms. These can be classified to two main groups, namely to solutions with one and more component(s), respectively. A drawback of the use of one-component solutions of trace elements is that a suitable background of instrumental analysis is necessary to determine the required amounts thereof, their use is complicated and expensive. According to the literature the composition of multicomponent trace-element solutions falls within narrow limits and practically, it follows the recommendations edited in 1979 in the United States of North America. [AMA Department of Foods and Nutrition: JAMA 241, 2051-2054 (1979)]. The composition of commercially available preparations practically corresponds to the recommendations mentioned above. These compositions may be exemplified e.g. by Trancitrans (manufactured by Fresenius; Ivemix Formula 01 (manufactured by Clintechnutrition Clinique); Tracutil (manufactured by Braun); Nonan (manufactured by Laboratoire Aguettant); and Addamel N (manufactured by Kabi).

A drawback of compositions commercially available and recommended by AMA is the unjustifiably high amount of manganese and molybdenum. Manganese deficiency rarely occurs
in patients fed in exclusively artificial route; at the same
time, manganese is easy to be accumulated in the body [A.
Ejima et al.: The Lancet 339, 426 (1992)] whereby a harmful
effect may be exerted on the brain and the nervous system.
Similarly, molybdenum deficiency infrequently occurs in
patients exclusively fed in artificial route: a single case
has only been reported in the literature during the last 30
years [D. A. Frankel: Nutrition Research 13, 583-596
(1993)]. Thus, the considerable molybdenum content of known
compositions is undue. An other disadvantage of the AMA
recommendations is that the amount of zinc is prescribed at
a too low level. Zinc-loss is considerable in patients
reduced to artificial nutrition and is accompanied by the
primary consequence that the patient cannot properly utilize
the food and he starves although the required amount of food
is available to him. When using the commercially available
compositions, zinc deficiency was frequently observed in the
body of the patients despite of the zinc content of the
composition [D. A. Frankel: Nutrition Research 13, 583-596
(1993)]. An additional drawback of known compositions is the
absence of magnesium. It is known that the magnesium loss of
patients needing artificial nutrition is significant. Thus,
disturbances of the cardiac function may occur, which result
in a considerably slower recovery of the patient [S. M.
Kobrin and S. Goldfarb: Seminars in Nephrology 10, 525-535
(1990); F. Perticone et al.: Magnesium Research 5, 265-272
(1992)].

A still further disadvantage of compositions used in the
practice is their sorbitol content. It is known that
sorbitol is counter-indicated to patients suffering from
fructose intolerance and its use is practically prohibited
for children since the lack of knowledge of a fructose
intolerance can induce adverse side-effects of fatal outcome
(1991); W. Heine: Infusiontherapie 18, 160-164 (1991); M. D.
Karlstad et al.: JPNEN 15, 445-449 (1991)].

The aim of the present invention is to eliminate the
drawbacks of the known compositions discussed above.
An other aim of the invention is to replace sorbitol used in known compositions by a component being biologically equivalent to but showing no side effects of sorbitol.

A still further aim of the invention is to prepare a trace element concentrate meeting the demands of human body, which can favourably be utilized for the preparation of infusion compositions extensively satisfying the needs of human body without the drawbacks of the known compositions.

Now, it has been found that xylitol can excellently be used for preparing infusion solutions of trace elements since no intolerance to this sugar alcohol is known and simultaneously, it effectively promotes the absorption of trace elements.

Furthermore, it has been found that the below-given composition having a reduced manganese and molybdenum content as well as a higher zinc and magnesium content can be used with good results in the preparation of infusion solutions and, when introduced to the human body, it does not show the disadvantages of known compositions.

Thus, the invention relates to a multicomponent aqueous concentrate, particularly for infusion compositions, which comprises macro- and trace elements and is characterized by xylitol content.

The aqueous concentrate according to the invention contains 10 to 4000 mg, preferably 100 to 2000 mg, particularly preferably 300 to 1000 mg, of xylitol related to 10 ml of solution.

From the aspect of the human body, the concentrate according to the invention contains the trace elements in favourable amounts and well-balanced ratios. Trace elements are essential constituents of the organism, co-factors of a number of enzymes and indispensable for the function of several biological processes. For these reasons, the supply of the organism forced to artificial nutrition with trace elements is of essential importance. When this is not satisfied with a proper efficiency, a number of symptoms and novel diseases will occur without any direct connection with the illness inducing the necessity of artificial nutrition.
Thus, due to the zinc deficiency, the organism is unable to utilize the foods introduced with the required efficiency, which then leads to the appearance of starvation symptoms.

Iron is an element of key importance for the respiratory and hematopoietic systems. Selenium represents an important component of protection to an oxidative stress attacking the body, wherein it enhances the efficiency of vitamin E among others. Molybdenum is a significant element of the amino acid metabolism. An important part of carbohydrate circulation in the body is chromium reducing among others the amount of insulin required to the incorporation of glucose usually employed in large amounts during artificial nutrition. Zinc is a highly important trace element being the co-factor of more than 300 enzymes which are inactivated by zinc deficiency. Copper is, among others, a promoting agent of number one of the bioavailability of iron and thereby it is an essential component of functioning of the respiratory and hematopoietic systems.

Trace elements can be most preferably administered in infusion solutions to the body of patients needing artificial nutrition. Due to the complex function of trace elements it is very important that the infusion solution contains these components in suitable amounts and ratios meeting the normal function of the organisms.

It has been found that aqueous trace-element concentrates containing 0.01 to 1.5 mg of copper, 0.005 to 0.5 mg of selenium, 0.1 to 20.0 mg of zinc and 1.0 to 100.0 mg of magnesium related to 10 ml of solution can very preferably be used for the preparation of infusion solutions.

Aqueous trace element concentrates containing 0 to 0.2 mg of manganese, 0 to 0.1 mg of molybdenum, 0.1 to 20.0 mg of zinc and 1.0 to 100 mg of magnesium related to 10 ml of solution are especially preferred.

The aqueous trace element concentrates of the invention contain preferably 0 to 0.18 mg, particularly preferably 0 to 0.15 mg, of manganese; preferably 0 to 0.02 mg, particularly preferably 0 to 0.009 mg, of molybdenum;
preferably 0.2 to 15.0 mg, particularly preferably 5.0 to 13.0 mg, of zinc; and preferably 10.0 to 90.0 mg, particularly preferably 40.0 to 80.0 mg, of magnesium related to 10 ml of solution.

The aqueous trace element concentrates of the invention may contain manganese, molybdenum, zinc and magnesium in the form of any of their water-soluble compounds which are innocuous to the organism. Manganese may preferably be present in the form of manganese(II) chloride, manganese(II) sulfate or manganese(II) gluconate. The compositions according to the invention may preferably contain molybdenum as ammonium molybdate or sodium molybdate. Zinc may preferably be present in the form of zinc chloride, zinc sulfate or zinc gluconate. The compositions of the invention may contain magnesium preferably in the form of magnesium chloride, magnesium sulfate, magnesium citrate or magnesium gluconate.

The trace element concentrates according to the invention may also comprise 0 to 0.5 mg of chromium, 0.01 to 1.5 mg of copper, 0 to 1.5 mg of fluorine, 0 to 2.0 mg of iron, 0 to 0.5 mg of iodine, 0.005 to 0.5 mg of selenium, 0 to 500.0 mg of calcium and 0 to 500.0 mg of phosphorus in relation to 10 ml of solution.

According to a preferred embodiment of the invention, the compositions may contain 0 to 0.02 mg of chromium, 0.02 to 1.1 mg of copper, 0 to 1.1 mg of fluorine, 0 to 1.8 mg of iron, 0 to 0.3 mg of iodine, 0.008 to 0.3 mg of selenium, 0 to 300.0 mg of calcium and 0 to 300.0 mg of phosphorus in relation to 10 ml of solution.

According to a particularly preferred embodiment of the invention, the compositions may contain 0 to 0.015 mg of chromium, 0.07 to 1.0 mg of copper, 0 to 1.0 mg of fluorine, 0 to 1.5 mg of iron, 0 to 0.15 mg of iodine, 0.008 to 0.25 mg of selenium, 0 to 280.0 mg of calcium and 0 to 220.0 mg of phosphorus in relation to 10 ml of solution.

The above-mentioned trace elements can be used in the form of any of their water-soluble compounds which are innocuous to the body. Thus, the aqueous trace element

SUBSTITUTE SHEET
concentrates according to the invention may contain chromium in the form of chromium(III) chloride or chromium(III) sulfate. Copper may preferably be present in the form of copper(II) chloride, copper(II) sulfate or copper(II) gluconate. The compositions may contain fluorine preferably as sodium fluoride or potassium fluoride. Iron may advantageously be present in the form of iron(II) sulfate, iron(III) sulfate, iron(III) citrate, iron(III) gluconate or iron(III) chloride. Iodine may preferably be added to the compositions in the form of sodium iodide or potassium iodide. Selenium may be present preferably in the form of sodium selenite, sodium selenate, selenous acid, selenomethionine or selenocysteine. The aqueous trace element concentrates of the invention may contain calcium preferably as calcium chloride or calcium gluconate. Phosphorus may be present preferably in the form of sodium dihydrogen phosphate, disodium hydrogen phosphate, potassium dihydrogen phosphate or trisodium phosphate.

The aqueous trace element concentrates of the invention are prepared by dissolving the macro- and trace elements as well as xylitol in water and adjusting the pH value between 0.8 and 4. The preferred pH value is between 1.5 and 2.5. The concentrate may be diluted by adding distilled water up to the desired final volume and then made isotonic by adding saline solution, if desired.

After dilution of the aqueous trace element concentrate with a suitable infusion solution, the infusion preparation obtained can be introduced to the body of the patient in the manner and by the means commonly used in the clinical practice.

Throughout in this description the amounts of macro- and trace elements are related to 10 ml of the concentrate. The daily dose is usually 0.5 to 25.0 ml, preferably 5.0 to 15.0 ml, especially preferably about 10 ml, of concentrate with the given composition.

The concentrate according to the invention is useful for preventing or eliminating, respectively, the deficiency of trace elements. The composition may advantageously be
utilized for the nutrition of patients suffering from severe burn injuries, for moderating the adverse side effects of chemotherapeutical treatments, for alleviating massive iron deficiency occurring during an intense treatment as well as for reducing the adverse side effects of an oxidative stress occurring to an enhanced degree during diseases.

The invention is illustrated in detail by the following non-limiting Examples.

Example 1

Components:

Chromium(III) chloride (CrCl₃·6H₂O) 5 mg
Copper(II) chloride (CuCl₂·2H₂O) 268 mg
Iron(III) chloride (FeCl₃·6H₂O) 581 mg
Potassium iodide (KI) 16 mg
Manganese(II) chloride (MnCl₂·4H₂O) 56 mg
Sodium molybdate (Na₂MoO₄·2H₂O) 2 mg
Sodium selenite (Na₂SeO₃) 7 mg
Zinc chloride (ZnCl₂) 42 mg
Sodium fluoride (NaF) 219 mg
Magnesium sulfate (MgSO₄·7H₂O) 15 g
Xylitol 50 g

The above components are dissolved in 600 ml of distilled water, the solution obtained is filled up to 1000 ml by adding distilled water while adjusting the pH value between 1.5 to 2.5.

Example 2

Components:

Chromium(III) chloride (CrCl₃·6H₂O) 0.4 mg
Copper(II) chloride (CuCl₂·2H₂O) 21 mg
Iron(III) chloride (FeCl₃·6H₂O) 193 mg
Sodium iodide (NaI) 0.5 mg
Manganese(II) chloride (MnCl₂·4H₂O) 1.5 mg
Sodium molybdate (Na₂MoO₄·2H₂O) 0.25 mg
Selenous acid (H₂SeO₃) 1.3 mg
Zinc chloride (ZnCl₂) 42 mg
Magnesium chloride (MgCl₂·6H₂O) 30 g
Potassium fluoride (KF) 12 mg
Calcium chloride (CaCl₂.2H₂O) 99 g
Disodium hydrogen phosphate (Na₂HPO₄.12H₂O) 243 g
Xylitol 50 g

After dissolving the above components in 600 ml of distilled water, the solution obtained is filled up to 1000 ml by adding distilled water while adjusting the pH value between 1.5 and 2.5.

Example 3

Components:
Copper(II) chloride (CuCl₂.2H₂O) 134 mg
Iron(III) chloride (FeCl₃.6H₂O) 484 mg
Manganese(II) chloride (MnCl₂.4H₂O) 30 mg
Sodium selenite (Na₂SeO₃) 60 mg
Zinc sulfate (ZnSO₄.7H₂O) 4.4 g
Magnesium chloride (MgCl₂.6H₂O) 50 g
Xylitol 50 g

After dissolving the above components in 600 ml of distilled water, the solution obtained is filled up to 1000 ml by adding distilled water while adjusting the pH value between 1.5 and 2.5.

Example 4

Components:
Copper(II) sulfate (CuSO₄.5H₂O) 393 mg
Iron(III) chloride (FeCl₃.6H₂O) 726 mg
Zinc sulfate (ZnSO₄.7H₂O) 3.5 g
Magnesium sulfate (MgSO₄.7H₂O) 81 g
Xylitol 50 g

After dissolving the above components in 600 ml of distilled water, the solution obtained is filled up to 1000 ml by adding distilled water while adjusting the pH value between 1.5 and 2.5.

Example 5

Components:
Copper(II) sulfate (CuSO₄.5H₂O) 196 mg
Zinc sulfate (ZnSO₄.7H₂O) 5.7 g

SUBSTITUTE SHEET
Magnesium sulfate (MgSO₄·7H₂O)  15 g
Xylitol  50 g

After dissolving the above components in 600 ml of distilled water, the solution obtained is filled up to 1000 ml by adding distilled water while adjusting the pH value between 1.5 and 2.5.

**Example 6**

Components:

Copper(II) sulfate (CuSO₄·5H₂O)  196 mg
Manganese(II) sulfate (MnSO₄·H₂O)  25 mg
Sodium selenite (Na₂SeO₃)  57 mg
Zinc sulfate (ZnSO₄·7H₂O)  5.7 g
Magnesium sulfate (MgSO₄·7H₂O)  50 g
Xylitol  50 g

After dissolving the above components in 600 ml of distilled water, the solution obtained is filled up to 1000 ml by adding distilled water while adjusting the pH value between 1.5 and 2.5.
Claims

1. A multicomponent aqueous concentrate containing macro- and trace elements particularly for infusion compositions, which comprises xylitol.

2. A composition as claimed in claim 1, which comprises 10 to 4000 mg of xylitol in relation to 10 ml of concentrate.

3. A composition as claimed in claim 2, which comprises 100 to 2000 mg of xylitol in relation to 10 ml of concentrate.

4. A composition as claimed in claim 3, which comprises 300 to 1000 mg of xylitol in relation to 10 ml of concentrate.

5. A composition as claimed in any of claims 1 to 4, which comprises 0.01 to 1.5 mg of copper, 0.005 to 0.5 mg of selenium, 0.1 to 20.0 mg of zinc and 1.0 to 100.0 mg of magnesium in relation to 10 ml if concentrate.

6. A composition as claimed in any of claims 1 to 5, which comprises 0 to 0.2 mg of manganese, 0 to 0.1 mg of molybdenum, 0.1 to 20.0 mg of zinc and 1.0 to 100.0 mg of magnesium in relation to 10 ml of concentrate.

7. A composition as claimed in any of claims 1 to 5, which comprises 0 to 0.2 mg of manganese, 0 to 0.1 mg of molybdenum, 0.1 to 20.0 mg of zinc and 0 to 100.0 mg of magnesium in relation to 10 ml of concentrate.

8. A composition as claimed in claim 6, which comprises 0 to 0.18 mg of manganese, 0 to 0.02 mg of molybdenum, 0.2 to 15 mg of zinc and 10.0 to 90.0 mg of magnesium in relation to 10 ml of concentrate.

9. A composition as claimed in claim 8, which comprises 0 to 0.15 mg of manganese, 0 to 0.009 mg of molybdenum, 5.0 to 13.0 mg of zinc and 40.0 to 80.0 mg of magnesium in relation to 10 ml of concentrate.

10. A composition as claimed in any of claims 6 to 9, which comprises manganese in the form of manganese(II) chloride, manganese(II) sulfate or manganese(II) gluconate.

11. A composition as claimed in any of claims 5 to 9,
which comprises molybdenum in the form of ammonium molybdate or sodium molybdate.

12. A composition as claimed in any of claims 6 to 9, which comprises zinc in the form of zinc chloride, zinc sulfate or zinc gluconate.

13. A composition as claimed in any of claims 6 to 9, which comprises magnesium in the form of magnesium chloride, magnesium sulfate, magnesium citrate or magnesium gluconate.

14. A composition as claimed in any of claims 11 to 13, which comprises 0 to 0.5 mg of chromium, 0.01 to 1.5 mg of copper, 0 to 1.5 mg of fluorine, 0 to 2.0 mg of iron, 0 to 0.5 mg of iodine, 0.005 to 0.5 mg of selenium, 0 to 500.0 mg of calcium and 0 to 500.0 mg of phosphorus in relation to 10 ml of concentrate.

15. A composition as claimed in claim 14, which comprises 0 to 0.02 mg of chromium, 0.02 to 1.1 mg of copper, 0 to 1.1 mg of fluorine, 0 to 1.8 mg of iron, 0 to 0.3 mg of iodine, 0.008 to 0.3 mg of selenium, 0 to 300.0 mg of calcium and 0 to 300.0 mg of phosphorus in relation to 10 ml of concentrate.

16. A composition as claimed in claim 15, which comprises 0 to 0.015 mg of chromium, 0.07 to 1.0 mg of copper, 0 to 1.0 mg of fluorine, 0 to 1.5 mg of iron, 0 to 0.15 mg of iodine, 0.008 to 0.25 mg of selenium, 0 to 280.0 mg of calcium and 0 to 220.0 mg of phosphorus in relation to 10 ml of concentrate.

17. A composition as claimed in any of claims 14 to 16, which comprises chromium in the form of chromium(III) chloride or chromium(III) sulfate.

18. A composition as claimed in any of claims 14 to 16, which comprises copper in the form of copper(II) chloride, copper(II) sulfate or copper(II) gluconate.

19. A composition as claimed in any of claims 14 to 16, which comprises fluorine in the form of sodium fluoride or potassium fluoride.

20. A composition as claimed in any of claims 14 to 16, which comprises iron in the form of iron(II) sulfate, iron(III) sulfate, iron(III) citrate, iron(III) gluconate or
iron(III) chloride.

21. A composition as claimed in any of claims 14 to 16, which comprises iodine in the form of sodium iodide or potassium iodide.

22. A composition as claimed in any of claims 14 to 16, which comprises selenium in the form of sodium selenite, sodium selenate, selenous acid, selenomethionine or selenocysteine.

23. A composition as claimed in any of claims 14 to 16, which comprises calcium in the form of calcium chloride or calcium gluconate.

24. A composition as claimed in any of claims 14 to 16, which comprises phosphorus in the form of sodium dihydrogen phosphate, disodium hydrogen phosphate, potassium dihydrogen phosphate or trisodium phosphate.

25. A process for the preparation of a multicomponent, aqueous concentrate containing macro- and trace elements, particularly for infusion compositions, which comprises dissolving the macro- and trace elements as well as xylitol in water and adjusting the pH value between 0.8 and 4.0.

26. A process as claimed in claim 25, which comprises adjusting the pH value between 1.5 and 2.5.

27. A process as claimed in claim 25 or 26, which comprises using 10 to 4000 mg of xylitol in relation to 10 ml of concentrate.

28. A process as claimed in claim 27, which comprises using 100 to 2000 mg of xylitol in relation to 10 ml of concentrate.

29. A process as claimed in claim 28, which comprises using 300 to 1000 mg of xylitol in relation to 10 ml of concentrate.

30. A process as claimed in any of claims 25 to 29, which comprises using 0.01 to 1.5 mg of copper, 0.005 to 0.5 mg of selenium, 0.1 to 20.0 mg of zinc and 1.0 to 100.0 mg of magnesium in relation to 10 ml of concentrate.

31. A process as claimed in any of claims 25 to 30, which comprises using 0 to 0.2 mg of manganese, 0 to 0.1 mg of molybdenum, 0.1 to 20.0 mg of zinc and 1.0 mg to 100.0 mg
of magnesium in relation to 10 ml of concentrate.

32. A process as claimed in claim 31, which comprises using 0 to 0.18 mg of manganese, 0 to 0.02 mg of molybdenum, 0.2 to 15 mg of zinc and 10.0 to 90.0 mg of magnesium in relation to 10 ml of concentrate.

33. A process as claimed in claim 32, which comprises using 0 to 0.15 mg of manganese, 0 to 0.009 mg of molybdenum, 5.0 to 13 mg of zinc and 40.0 mg to 80.0 mg of magnesium in relation to 10 ml of concentrate.

34. A process as claimed in any of claims 31 to 33, which comprises using manganese in the form of manganese(II) chloride, manganese(II) sulfate or manganese(II) gluconate.

35. A process as claimed in any of claims 31 to 33, which comprises using molybdenum in the form of ammonium molybdate or sodium molybdate.

36. A process as claimed in any of claims 31 to 33, which comprises using zinc in the form of zinc chloride, zinc sulfate or zinc gluconate.

37. A process as claimed in any of claims 31 to 33, which comprises using magnesium in the form of magnesium chloride, magnesium sulfate, magnesium citrate or magnesium gluconate.

38. A process as claimed in any of claims 25 to 37, which comprises using 0 to 0.5 mg of chromium, 0.01 to 1.5 mg of copper, 0 to 1.5 mg of fluorine, 0 to 2.0 mg of iron, 0 to 0.5 mg of iodine, 0.005 to 0.5 mg of selenium, 0 to 500.0 mg of calcium and 0 to 500.0 mg of phosphorus in relation to 10 ml of concentrate.

39. A process as claimed in claim 38, which comprises using 0 to 0.02 mg of chromium, 0.02 to 1.1 mg of copper, 0 to 1.1 mg of fluorine, 0 to 1.8 mg of iron, 0 to 0.3 mg of iodine, 0.008 to 0.3 mg of selenium, 0 to 300.0 mg of calcium and 0 to 300.0 mg of phosphorus in relation to 10 ml of concentrate.

40. A process as claimed in claim 39, which comprises using 0 to 0.015 mg of chromium, 0.07 to 1.0 mg of copper, 0 to 1.0 mg of fluorine, 0 to 1.5 mg of iron, 0 to 0.15 mg of iodine, 0.008 to 0.25 mg of selenium, 0 to 280.0 mg of
calcium and 0 to 220.0 mg of phosphorus in relation to 10 ml of concentrate.

41. A process as claimed in any of claims 38 to 40, which comprises using chromium in the form of chromium(III) chloride or chromium(III) sulfate.

42. A process as claimed in any of claims 38 to 40, which comprises using copper in the form of copper(II) sulfate or copper(II) gluconate.

43. A process as claimed in any of claims 38 to 40, which comprises using fluorine in the form of sodium fluoride or potassium fluoride.

44. A process as claimed in any of claims 38 to 40, which comprises using iron in the form of iron(II) sulfate, iron(III) sulfate, iron(III) citrate, iron(III) gluconate or iron(III) chloride.

45. A process as claimed in any of claims 38 to 40, which comprises using iodine in the form of sodium iodide or potassium iodide.

46. A process as claimed in any of claims 38 to 40, which comprises using selenium in the form of sodium selenite, sodium selenate, selenous acid, selenomethionine or selenocysteine.

47. A process as claimed in any of claims 38 to 40, which comprises using calcium in the form of calcium chloride or calcium gluconate.

48. A process as claimed in any of claims 38 to 40, which comprises using phosphorus in the form of sodium dihydrogen phosphate, disodium hydrogen phosphate, potassium dihydrogen phosphate or trisodium phosphate.

49. A method for preventing the development of trace element deficiency, eliminating trace element deficiency, nutrition of patients suffering from severe burn injuries, moderating the adverse side effects of chemotherapeutical treatments, alleviating massive iron deficiency occurring during an intensive therapy and moderating the adverse side effects of an oxidative stress occurring to an enhanced degree during diseases, which comprises administering a therapeutically effective amount of a concentrate according
to claim 1 in a suitable infusion solution to a patient suffering from the above diseases or showing the above symptoms.

50. An infusion solution which comprises an aqueous trace element concentrate according to any of claims 1 to 24.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC: A 61 K 31/70, 79/08, 33/00, 33/33, 30/33, 34/33, 33/24, 34/33, 42, 33/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A 61 K 31/00, 9/00, 33/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>US 5 108 754 A (WILBURN M.) 28 April 1992 (28.04.92), claims 1-3, 5, 6, 8, 9, 11, 12; column 11, lines 7-37; column 8, line 31 - column 9, line 47.</td>
<td>1-18, (19), 20-24, 25-42, (43), 44-50</td>
</tr>
<tr>
<td>DE 39 43 424 A1 (NEPHRO-MEDICA PHARMAZENTISCHE VERTRIEBSGESELLSCHAFT MBH) 04 July 1991 (04.07.91),</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C. See patent family annex.

- Special categories of cited documents:
  - "A" document defining the general state of the art which is not considered to be of particular relevance
  - "E" earlier document but published on or after the international filing date
  - "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
  - "O" document referring to an oral disclosure, use, exhibition or other means
  - "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

Date of the actual completion of the international search
05 July 1995 (05.07.95)

Date of mailing of the international search report
20 July 1995 (20.07.95)

Name and mailing address of the ISA/AT
AUSTRIAN PATENT OFFICE
Kohlmarkt 8-10
A-1014 Vienna
Facsimile No. 1/53424/535

Authorized officer
Mazzucco e.h.
Telephone No. 1/5337058/33

Form PCT/ISA/210 (second sheet) (July 1992)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>abstract; claims 1,5,7,10; page 5, lines 16-27.</td>
<td>1-4, 6-9, 12-13,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>25-29, 31-33, 36-37,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>49, 50 (partially)</td>
</tr>
<tr>
<td>Y</td>
<td>totality; especially claims 1-15; page 2, lines 4-35; pages 3-14.</td>
<td>5, 10, 11, 14-24,</td>
</tr>
<tr>
<td></td>
<td>EP 0 306 377 A1 (CHRISTOPHE C.) 08 March 1989 (08.03.89).</td>
<td>30, 34, 35, 38-48,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 (partially)</td>
</tr>
<tr>
<td>Y</td>
<td>EP 0 190 459 A1 (PFRIEMER &amp; CO.) 13 August 1986 (13.08.86), abstract; claims 1-3.</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>1-4, 25-29, 49,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 (partially)</td>
</tr>
<tr>
<td>Y</td>
<td>US 4 871 550 A (MILLMAN P.L.) 03 October 1989 (03.10.89), claims; column 8, lines 32-45; column 9, line 22 - column 10, line 22.</td>
<td>5-24, 30-48, 50 (partially)</td>
</tr>
<tr>
<td>X</td>
<td>DE 19 20 730 B (OTSUKA PHARM.CO.LTD.) 20 July 1972 (20.07.72), columns 1-3.</td>
<td>1-4, (24), 25-29,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(48), 49, 50 (partially)</td>
</tr>
<tr>
<td>X</td>
<td>WO 82/03 552 A1 (AMERICAN HOSPITAL SUPPLY CORPORATION) 28 October 1982 (28.10.82), claims 1,4,11,15,19,20, 23,26,29,33,39-41.</td>
<td>1-4, 25-29, 49,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>50 (partially)</td>
</tr>
<tr>
<td>X</td>
<td>DE 19 55 245 A (ABBOTT LAB.) 11 June 1970 (11.06.70), claims 1,2.</td>
<td>1-4, 49, 50 (partially)</td>
</tr>
<tr>
<td>X</td>
<td>WO 92/10 997 A1 (EBY G.A.) 09 July 1992 (09.07.92), abstract; claims 1,3,8,9,12,13; page 8, lines 4-22; page 15, line 14 - page 16, line 26; page 21, lines 25-34; page 23, lines 25-36.</td>
<td>1-4, 7, 13, 25-29, 37,49</td>
</tr>
<tr>
<td>X</td>
<td>US 4 201 706 A (S.F. TRAGER) 06 May 1980 (06.05.80), claims 1-3,8,9; column 2, lines 41-55.</td>
<td>1-4</td>
</tr>
</tbody>
</table>
INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. X Claims Nos.: please see remark because they relate to subject matter not required to be searched by this Authority, namely:

   Although claim 49 is directed to a method of treatment of the human or animal body by therapy (see Rule 39.1 iv PCT) the search has been carried out and based on the alleged effects of the concentrate.

2. ☐ Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II  Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest ☐ The additional search fees were accompanied by the applicant’s protest.
☐ No protest accompanied the payment of additional search fees.
<table>
<thead>
<tr>
<th>Document de brevet cité dans le rapport de recherche</th>
<th>Datum der Veröffentlichung</th>
<th>Mitglieder der Patentfamilie</th>
<th>Datum der Veröffentlichung</th>
</tr>
</thead>
<tbody>
<tr>
<td>US A 5108754</td>
<td>28-04-92</td>
<td>AP A 9200358</td>
<td>30-04-92</td>
</tr>
<tr>
<td></td>
<td></td>
<td>BR A 5205690</td>
<td>26-07-94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA A 2105980</td>
<td>09-08-94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP A 571474</td>
<td>01-12-94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IT A 1006663</td>
<td>06-09-94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP T2 6237382</td>
<td>26-08-94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US A 5177208</td>
<td>05-01-93</td>
</tr>
<tr>
<td>DE A1 3943424</td>
<td>04-07-91</td>
<td>keine - none - rien</td>
<td></td>
</tr>
<tr>
<td>EP A1 306377</td>
<td>08-03-89</td>
<td>AT E 72984</td>
<td>15-03-89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU B A 2046488</td>
<td>28-02-89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CH A 4576684</td>
<td>22-10-89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE A 3656871</td>
<td>04-03-93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP B1 3036377</td>
<td>03-04-93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ES T2 2004712</td>
<td>17-04-93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FR A1 2665231</td>
<td>27-12-89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP A5 190459</td>
<td>19-04-94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US A 5091369</td>
<td>22-02-92</td>
</tr>
<tr>
<td>US A 4871550</td>
<td>03-10-89</td>
<td>EP A2 59146</td>
<td>09-03-90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US A 5091369</td>
<td>14-03-90</td>
</tr>
<tr>
<td>DE B1 1920730</td>
<td>12-11-79</td>
<td>DE A3 5091369</td>
<td>18-10-89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE CS 1920730</td>
<td>12-11-89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>IT A 1476749</td>
<td>26-11-82</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP T2 5800562</td>
<td>07-04-83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>keine - none - rien</td>
<td></td>
</tr>
<tr>
<td>DE A1 1955245</td>
<td>11-06-71</td>
<td>keine - none - rien</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU A 9126094</td>
<td>08-06-93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA A 2505870</td>
<td>26-06-93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP A 5666338</td>
<td>22-10-93</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US A 5095025</td>
<td>26-03-94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US A 5095025</td>
<td>26-03-94</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US A 4955355</td>
<td>11-09-90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>US E 33465</td>
<td>27-11-90</td>
</tr>
</tbody>
</table>

Form PCT/ISA/210 (patent family annex) (July 1992)