

Nutrition

# Influence of the glass packing on the contamination of pharmaceutical products by aluminium. Part III: Interaction container-chemicals during the heating for sterilisation

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## Abstract

The interaction of chemicals with the container materials during heating for sterilisation was investigated, storing the components of parenteral nutrition solutions individually in sealed glass ampoules and in contact with a rubber stopper, and heating the system at 121 °C for 30 min. Subsequently, the aluminium content of the solutions was measured by atomic absorption spectrometry (AAS). The assay was also carried out with acids, alkalis and some complexing agents for Al. The containers were decomposed and also assayed for aluminium. 30 different commercial solutions for parenteral nutrition, stored either in glass or in plastic containers, were assayed measuring the aluminium present in the solutions and in the container materials. The results of all investigated container materials revealed an aluminium content of 1.57% Al in glass, 0.05% in plastic and 4.54% in rubber. The sterilisation procedure showed that even pure water was able to extract Al from glass and rubber,  $22.5 \pm 13.3 \mu\text{g/L}$  and  $79.4 \pm 22.7 \mu\text{g/L}$  respectively, while from plastic the aluminium leached was insignificant. The Al released from glass ampoules laid between 20  $\mu\text{g/L}$  for leucine, ornithine and lysine solutions and 1500  $\mu\text{g/L}$  for solutions of basic phosphates and bicarbonate; from rubber stoppers it reached levels over 500  $\mu\text{g/L}$  for cysteine, aspartic acid, glutamic acid and cystine solutions. Ion-exchange properties and influence of pH can explain the interaction of glass with some chemicals (salts, acids and alkalis), but only an affinity for aluminium could explain the action of some amino acids and other chemicals, as albumin and heparin, on glass and rubber, considering the aluminium release. Experiments with complexing agents for Al allowed to conclude that the higher the stability constant of the complex, the higher the Al release from the container material.

**Key words:** aluminium, contamination, glass, rubber, sterilisation, parenteral nutrition

## Introduction

Parenteral nutrition (PN) is the administration of nutrients intravenously to patients that cannot be fed via gas-

trointestinal tract. Products for parenteral nutrition are commercialised in form of sterile solutions, and include electrolytes (Na, K, Ca, Mg, chloride, bicarbonate, acetate and phosphate), amino acids, carbohydrates (glucose and polyols), oligoelements (Cu, Zn, Cr, Mn), albumin, vitamins and lipids. Although the presence of Al in pharmaceutical products used parenterally is known at least for 18 years (1, 2), this is still an unsolved problem today.

Al has a toxic effect to children and adults with chronic renal failure and to patients on long-term parenteral

**Dedicated to Professor Dr. Georg Schwedt on the occasion of his 60<sup>th</sup> birthday.**

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nutrition (3–7). Moreover, Al can also be associated with impaired neurologic development in preterm infants, which receive prolonged intravenous feeding (8–11).

The American Societies for Clinical Nutrition (ASCN), for Parenteral and Enteral Nutrition (ASPEN) (12) and for Pediatric Gastroenterology and Nutrition (ASPGN) (13) proposed to restrict the Al contamination of large volume parenterals to a maximum of 25 µg/L, and although for small volume parenterals no maximum level was proposed, the label should inform how many µg Al/L the product contains. Studies have been showing, however, that Al found in these formulations is almost always over the proposed limit (14–16).

Several investigations (17–20) dealt with the presence of Al in these formulations but none of them offered explanations for the origin of the Al contamination. The results found by all authors revealed, however, that Al in these products can reach levels over 5000 µg/L, and that even being produced by different manufacturers and in different countries, the distribution of the contamination in these products is the same: calcium gluconate, phosphate salts and oligoelements are the most contaminated, followed by vitamins and albumin, while dextrose and amino acids are among the least contaminated.

Two possible sources can be suspected of contributing to the presence of Al in these products: raw material and containers, not considering any step of the industrial processing of these formulations. In spite of the high probability of the contamination by these sources, we found only two papers which related the contamination of albumin (21) and gluconate (22) solutions to their storage in glass containers.

In previous works we investigated the influence of the storage time of the solutions in contact with the glass and plastic surface of the containers considering the shelf-life of the products (23, 24), and the contribution of the Al present as impurity in the chemicals to the contamination of the solutions for PN (25).

In the present work we investigated glass, plastic and rubber as container materials considering their interaction with the chemicals and possible Al releasing during the heating for the sterilisation procedure.

## Experimental

### Apparatus

A Varian SpectrAA-200 atomic absorption spectrometer equipped with a GTA-100 graphite furnace and an autosampler (Melbourne, Australia), a Trox class 100 clean bench (Curitiba, Brasil), a Phoenix AV 50 N 6281 autoclave (São Paulo, Brasil), a Berghof BSB 939-IR sub-boiling distillation apparatus (Eningen, Germany) and a Digimed pHmeter D-20 (São Paulo, Brasil) were used.

### Reagents

The water used throughout was distilled, deionised and further purified by a Milli-Q high purity water device (Millipore, Bedford, USA). An Al standard solution containing 1000 mg/L Al (Merck, Germany) was used to prepare the

working standard solutions. HNO<sub>3</sub> (65%, 1.40 g/mL) from Merck was further purified by sub-boiling distillation.

### Contamination control

To avoid contamination, only plastic materials were used. All laboratory ware (pipette tips, volumetric flasks, etc.) were immersed for at least 48 h in a 10% (v/v) HNO<sub>3</sub>/ethanol solution and washed with Milli-Q purified water shortly before use.

To avoid contamination from the air, all steps in the sample and reagent preparation were carried out in a class 100 clean bench.

### Procedures

The assayed chemicals included besides salts, amino acids, glucose, albumin, heparin and some polyols used in parenteral nutrition: acetic acid, hydrochloric acid, sodium hydroxide, sodium nitrate, sulfate and gluconate, calcium chloride, magnesium chloride, zinc chloride, manganese chloride, copper chloride, chromium chloride, and the complexing agents for Al EDTA, NTA, oxalic acid and citric acid. Although heparin is not used for parenteral nutrition, it was included in the experiment. The salts above cited that are not used in parenteral nutrition were included in the experiment in order to compare the influence of different cations and anions on the interaction with the container material. The substances were of "for analysis" quality and from different manufactures (Merck, Sigma, Aldrich, Riedel-de Haën or Ajinomoto). For the analysis, solutions containing 0.1, 1.0 or 10.0% (m/v) of the substance were prepared in polyethylene volumetric flasks, and the Al content measured by flame or electrothermal atomic absorption spectrometry (FAAS or ETAAS, respectively), following the conditions described in Table 1. The chloride containing solutions were analysed directly by FAAS or by ETAAS, after a treatment to separate the saline matrix according to a method earlier described (26), because chloride ions cause interferences on graphite furnace measurements.

Solutions of amino acids were also prepared 0.1, 1.0 or 10.0% (m/v) according to their solubility or Al content. For the amino acids which solubility did not allow complete dissolution, HNO<sub>3</sub> was added to promote the solubilisation.

Heparin was dissolved to give a solution with the same concentration (5000 UI/mL) as the commercial product.

All samples were prepared in triplicates and the measurement was carried out just after the preparation.

### Analysis of the containers

Polyethylene ampoules (10 and 20 mL), glass ampoules (10 and 20 mL), bottles for amino acid solutions (100, 250 and 500 mL), and grey and red elastomeric closures for amino acid bottles, all from commercial products, were assayed for their Al content.

The glass containers were crushed into fragments about 1 mm in size and well mixed. One hundred milligrams of the glass fragments was placed in a PTFE vessel with 5 mL of 48% (m/m) hydrofluoric acid and 5 mL of water, and heated in a domestic microwave oven at a minimal power

(174 W) for 10 min. The procedure was repeated twice. After the total dissolution of the sample the volume was completed to 200 mL with water and Al measured by FAAS.

The plastic ampoules were cut into small pieces and a portion of 1 g was mixed with approximately 2 g of  $\text{KNO}_3$  and heated in a platinum crucible at 250 °C for 3 hours. The ash was dissolved in 4 mL of 96% (m/m)  $\text{H}_2\text{SO}_4$  and diluted to 50 mL with water. Al was measured by FAAS.

The decomposition of the rubber stoppers was carried out by heating 0.2 g of the rubber in a platinum crucible at 600 °C for 2 hours. The ash was dissolved by addition of 6 mL hydrofluoric acid 1+1 with water, and gently heated. The final volume was made up to 100 mL with water. The Al measurement was carried out by FAAS.

A blank experiment was carried out using only the reagents and including all steps of the three different decomposition procedures.

#### Preparation of the samples for moist heat sterilisation

As the analysis revealed a very low level of Al in plastic containers, the heating procedure was carried out only with glass containers; moreover, the usual procedure for sterilising parenterals in plastic containers is not through heat but by using ethylene dioxide or radiation (27).

10 mL new glass ampoules for injectables (Schott do Brasil) were filled with a 0.5% (m/v) solution of each substance selected for the assay. The ampoules were sealed and heated at 121 °C in an autoclave for 30 min. After cooling down they were opened and the Al content

of the solution measured by FAAS or ETAAS. The Al already present in the substances was discounted from the Al measured. The experiment was carried out in triplicates. Twelve ampoules filled only with pure water were also submitted to the sterilisation procedure. Three new ampoules were assayed individually for their Al content as described in the previous section.

#### Closure experiments

Among the investigated commercial products for parenteral nutrition only the amino acids and albumin solutions were stored in bottles with elastomeric closures. Therefore the assay was carried out with amino acid solutions, and also with the complexing agents EDTA, NTA, citric acid and oxalic acid, and with hydrochloric acid, acetic acid and sodium hydroxide. A rubber stopper (grey) was stored individually in 200 mL of each solution in a polypropylene flask and submitted to the sterilisation procedure as described above. The assay was also carried out with the closure in contact with pure water. The experiments were carried out in triplicates. Three pieces of these closures were also assayed to determine their Al content.

#### Analysis of commercial products

Commercial solutions of salts, glucose, heparin and albumin and formulations containing amino acids were analysed. With the exception of 10% and 20% NaCl, 10% and 19.1% KCl and ampoules of oligoelements (Zn, Cu, Cr and Mn salts), the Al was measured directly by FAAS or ETAAS (some samples had to be diluted to have their Al concentration in the range of the calibration curves). The Al present in these salt solutions was determined according to the method mentioned above, after matrix separation (26). For all products, at least 3 samples of the same batch were analysed, and the reported results correspond to the mean value calculated from these replicates.

## Results

#### Containers and closures

The analysis of containers and closures used for storing of commercial parenteral solutions showed that Al was present in all three types of materials: plastic, glass and rubber (Table 2). However, whereas in plastic containers only a small amount was found, probably from catalysts used for plastic polymerisation, Al is present in high levels in glass and rubber. Aluminium oxide is added to glass to improve its chemical resistance, so that glass for parenterals contains normally from 2.6 to 6.6%  $\text{Al}_2\text{O}_3$  (28). Rubber can contain Al as well. Hydrate or calcined aluminium silicate (clay) is used as filler in elastomeric materials to improve hardness, abrasion resistance and density (29). In spite of the fact that other materials can be used as filler, Al was found in all rubber analysed in this work.

#### Sterilisation

The ampoules used for this experiment presented an Al level of  $2.14 \pm 0.47\%$ .

**Table 1.** Atomic absorption spectrometer operating conditions.

|                                                                     |                  |          |                  |
|---------------------------------------------------------------------|------------------|----------|------------------|
| <i>Instrument</i>                                                   |                  |          |                  |
| Wavelength (nm)                                                     | 309.3            |          |                  |
| Lamp current (mA)                                                   | 10               |          |                  |
| Spectral slit width (nm)                                            | 0.5              |          |                  |
| Background correction                                               | Deuterium lamp   |          |                  |
| <i>Flame</i>                                                        |                  |          |                  |
| Acetylene/nitrous oxide                                             |                  |          |                  |
| <i>Graphite furnace</i>                                             |                  |          |                  |
| Pyrolytic coated furnace with L'vov platform and argon as purge gas |                  |          |                  |
| <i>Temperature programme</i>                                        |                  |          |                  |
| Step                                                                | Temperature (°C) | Time (s) | Gas flow (L/min) |
| 1                                                                   | 85               | 5        | 3.0              |
| 2                                                                   | 95               | 35       | 3.0              |
| 3                                                                   | 120              | 10       | 3.0              |
| 4                                                                   | 1100             | 20       | 3.0              |
| 5                                                                   | 1100             | 10       | 3.0              |
| 6                                                                   | 1100             | 2        | 0.0              |
| 7*                                                                  | 2500             | 0.7      | 0.0              |
| 8*                                                                  | 2500             | 1        | 0.0              |
| 9                                                                   | 2600             | 1        | 3.0              |

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**Table 2.** Aluminium present as contaminant in commercial parenteral solutions and in container materials. All solutions were within their guaranteed period of shelf-life.

| Product                      | Al in solution<br>±SD (µg/L) | Container      | Al in container<br>(%) |
|------------------------------|------------------------------|----------------|------------------------|
| NaCl 20%                     | 149 ± 10                     | glass ampoule  | 1.43                   |
|                              | 13 ± 4                       | polyethylene   | 0.04                   |
| KCl 10%                      | 68 ± 6                       | glass ampoule  | 1.25                   |
|                              | 23 ± 5                       | polyethylene   | 0.06                   |
| Magnesium sulfate 50%        | 560 ± 85                     | glass ampoule  | 1.25                   |
|                              | 380 ± 288                    | glass ampoule  | 1.43                   |
| Sodium acetate 2 meq/mL      | 45 ± 7                       | glass ampoule  | 2.14                   |
|                              | 17 ± 8                       | polyethylene   | 0.05                   |
| Potassium phosphate 2 meq/mL | 988 ± 76                     | glass ampoule  | 1.98                   |
|                              | 1325 ± 142                   | glass ampoule  | 2.45                   |
| Sodium phosphate 0.5 mol/L   | 933 ± 88                     | glass ampoule  | 1.65                   |
|                              | 879 ± 203                    | glass ampoule  | 2.05                   |
| Calcium gluconate 10%        | 5621 ± 1165                  | glass ampoule  | 1.51                   |
|                              | 5960 ± 62                    | glass ampoule  | 2.21                   |
| Sodium bicarbonate 8.4%      | 833 ± 141                    | glass bottle   | 0.99                   |
|                              | 922 ± 102                    | glass bottle   | 1.03                   |
| Oligoelements <sup>a</sup>   | 1129 ± 33                    | glass ampoule  | 2.14                   |
| Oligoelements <sup>b</sup>   | 1854 ± 744                   | glass ampoule  | 2.21                   |
| Amino acids 10%              | 164 ± 6                      | glass bottle   | 0.82                   |
|                              |                              | rubber closure | 3.91                   |
| Amino acids 10%              | 116 ± 30                     | glass bottle   | 0.76                   |
|                              |                              | rubber closure | 4.23                   |
| Amino acids 10%              | 93 ± 23                      | glass bottle   | 0.84                   |
|                              |                              | rubber closure | 5.34                   |
| Amino acids 10%              | 65 ± 13                      | glass bottle   | 0.89                   |
|                              |                              | rubber closure | 5.70                   |
| Amino acids 10%              | 23 ± 8                       | plastic bag    | 0.01                   |
| Glucose 50%                  | 13 ± 1                       | polyethylene   | 0.04                   |
|                              | 293 ± 14                     | glass ampoule  | 1.15                   |
| Glucose 25%                  | 9 ± 3                        | polyethylene   | 0.08                   |
|                              | 370 ± 23                     | glass ampoule  | 1.87                   |
| Albumin 20%                  | 644 ± 58                     | glass flask    | 0.67                   |
|                              |                              | rubber closure | 4.06                   |
|                              | 149 ± 23                     | glass flask    | 0.66                   |
|                              |                              | rubber closure | 3.99                   |
| Heparin 5000 UI/mL           | 732 ± 23                     | glass ampoule  | 2.88                   |
|                              | 738 ± 54                     | glass ampoule  | 3.03                   |

<sup>a</sup> Composition: 22.0 mg ZnSO<sub>4</sub>, 6.3 mg CuSO<sub>4</sub>, 2.46 mg MnSO<sub>4</sub>, 102.5 µg CrCl<sub>3</sub> per ampoule

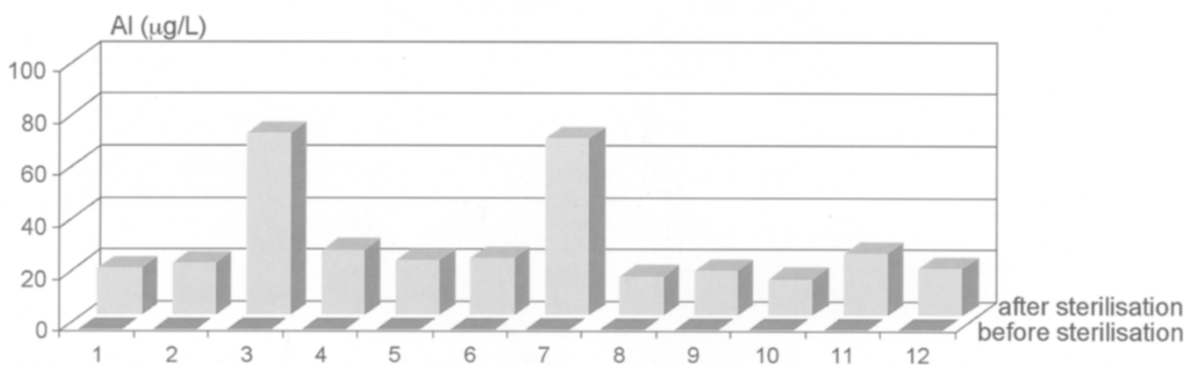
<sup>b</sup> Composition: 8.8 mg ZnSO<sub>4</sub>, 1.60 mg CuSO<sub>4</sub>, 123.04 µg MnSO<sub>4</sub>, 20.50 µg CrCl<sub>3</sub> per ampoule

Suppliers: Abbott, Ariston, Aster, Baxter, Behring, B. Braun, Darrow, Fresenius, Fujisawa, Gayer, Halex Istar, Hypofarma, Santisa, Roche, Zenalb

The first step of the investigation on Al release from glass during the sterilisation procedure was carried out with pure water. The results of ampoules filled only with water showed that even pure water is capable to extract Al from the glass surface (Fig. 1). A mean value of  $22.5 \pm 13.3$  µg/L Al was measured in the water samples after heating for sterilisation.

Fig. 2 shows the Al extracted from glass ampoules filled with solutions of the different investigated substances during the moist heat procedure. Among the salt solutions, those having a basic character showed the highest interaction. Whereas chlorides and sulfates extracted a mean of 200 µg/L Al, basic phosphates and bicarbonate extracted more than 900 µg/L Al (see also Fig. 3a). Al released by the NaOH solution (4500 µg/L) confirms the stronger interaction of the alkaline solutions with glass. Among the amino acids, there were some that did not extract Al from the glass ampoule, and others that were able to extract a large amount of Al. Solutions of cystine, cysteine, aspartic acid, glutamic acid and tyrosine extracted more than 200 µg/L respectively, whereas solutions of lysine, ornithine and leucine extracted as much Al as pure water. Fig. 2 also shows Al extracted by action of complexing agents and the polyols mannitol, sorbitol and xylitol.

Fig. 3 shows Al extracted by action of salts, grouped according to their constituents: different anions having the same cation in Fig. 3a, and different cations bound to the same anion in Fig. 3b. For this comparison, salts not used in parenterals were included; the aim was to evaluate the action of cations and anions respectively. Con-

**Fig. 1.** Aluminium extracted from glass ampoules during sterilisation at 121 °C for 30 min by action of pure water.

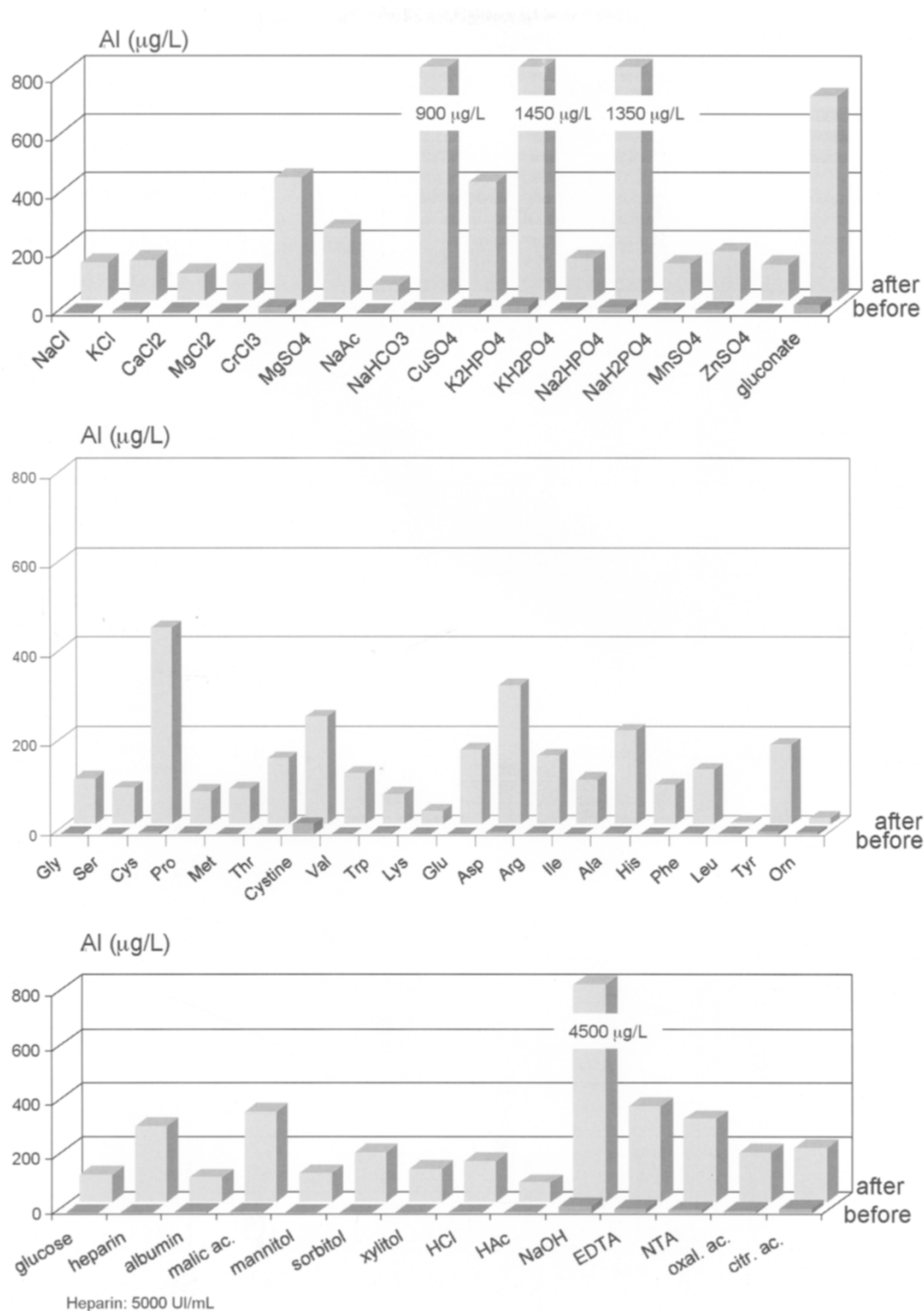


**Fig. 2.** Aluminium extracted from glass ampoules during sterilisation at 121 °C for 30 min by action of solutions of different substances at a concentration of 0.5% (m/v). Results are a mean of three replicates. After = after sterilisation, before = before sterilisation.

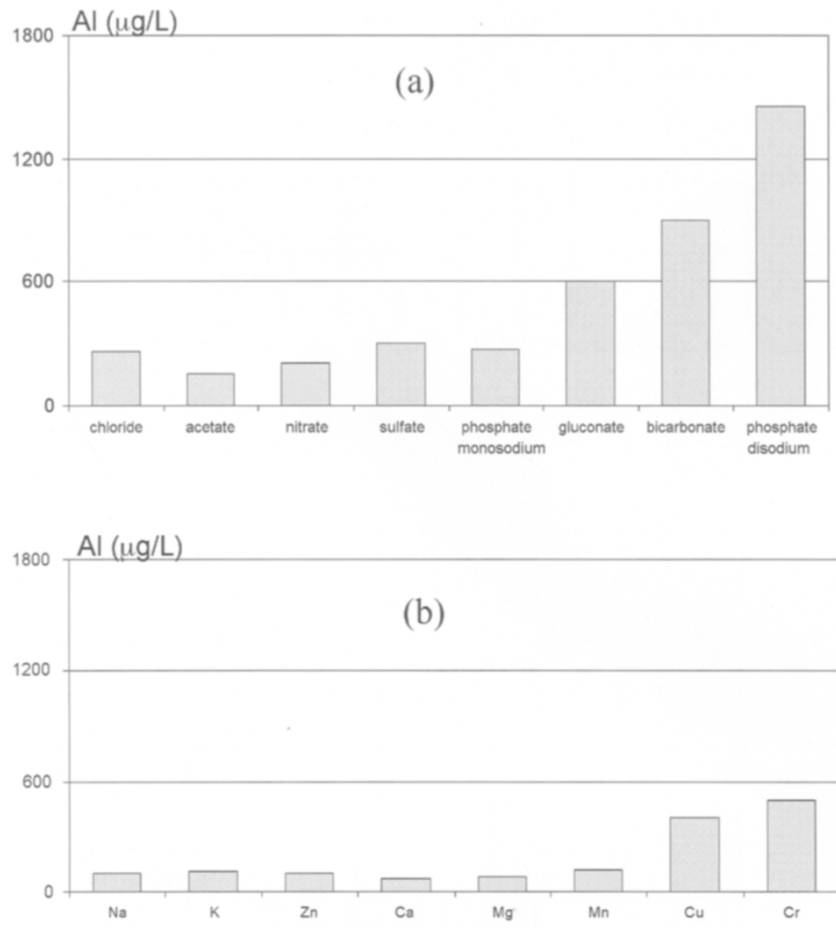


**Fig. 3.** Comparison of aluminium extracted from glass ampoules by action of different cations and anions. (a) sodium salts of different anions, (b) chloride salts of different cations.

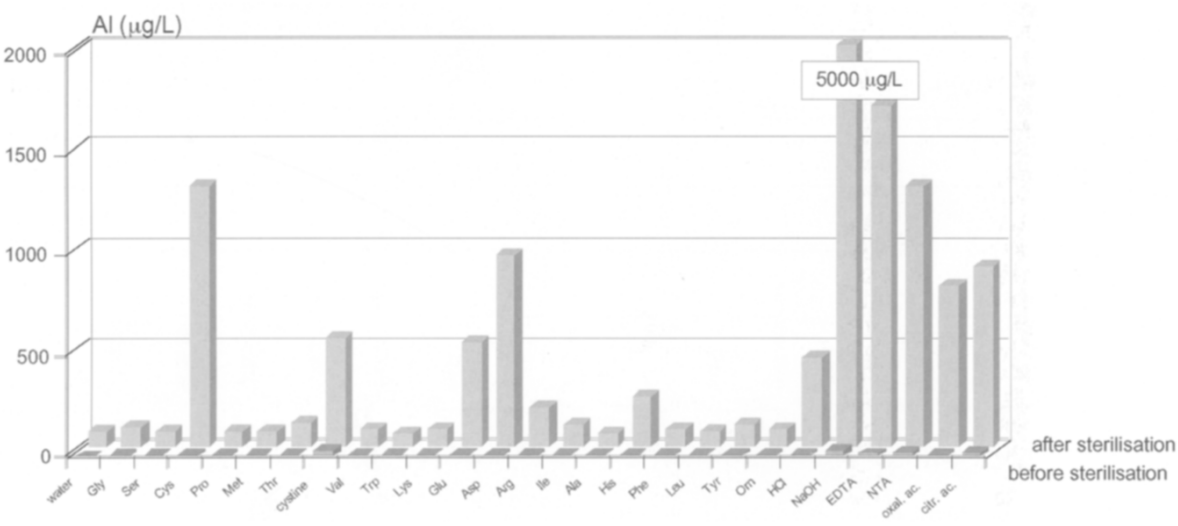


**Fig. 4.** Aluminium extracted from grey rubber closure during sterilisation at 121 °C for 30 min by action of water, amino acids and complexing agents. Results are a mean of three replicates. Concentration of the solutions: 0.5% (m/v).

sidering the anions, the dibasic phosphates, bicarbonate and gluconate interacted strongest, whereas among cations, the higher extraction occurred in solutions of chromium and copper salts.

Fig. 4 shows Al extracted from the elastomeric closures by action of water, amino acid and complexing agent solutions. It can be seen that the same behaviour, observed for the sterilisation of amino acid and complexing agent solutions in contact with glass containers, occurred with the closures. Whereas cystine, cysteine, aspartic acid and glutamic acid interacted with rubber and withdrew Al, almost all other amino acid solutions had the same effect as pure water, i. e. they did not play any role in extracting Al from the material.

### Commercial solutions

Table 2 shows the results of the analysis of some commercial products. Gluconate and phosphate salts were among the most contaminated as already found by other authors. Also the oligoelement solutions were highly contaminated by Al. Unfortunately, we did not find calcium gluconate, phosphates and oligoelements commercialised in plastic containers, therefore no comparison between these products stored in glass and plastic containers was possible. The investigation of the other products showed clearly, that the same formulation can be more or less contaminated by Al depending on the container material.

As can be seen in Table 2, all products stored in glass containers were more contaminated than the same products stored in plastic containers. However, among the products in glass containers, different contamination levels were found, with the same distribution observed in solutions of these substances after the sterilisation procedure carried out in this work.

## Discussion

The aim of this work was to show that the action of chemicals on the container material could lead to an Al release into the solution, accelerated by the heat during the sterilisation procedure. This investigation was carried out only with glass containers and rubber stoppers, because the Al content measured in plastic containers was too low to contribute to the contamination of the solution. The results revealed that the heating of the solutions in contact with glass and rubber could lead to a contamination of the products by Al.

However, the action of chemicals on glass and rubber depends on their nature; the three following properties of a solution can lead to Al release: pH of the solution, similarity between Al and any cation in the solution, and affinity to Al.

The dissolving action of alkaline solutions on glass surfaces is known (30). Hydroxyl ions react with silica, according to the reaction:  $4\text{OH}^- + \text{SiO}_2 \rightarrow \text{SiO}_4^{4-} + 2\text{H}_2\text{O}$ . As Al also exists as an oxide in the glass structure and reacts with hydroxyl ions in the same way as silica,  $4\text{OH}^- + \text{Al}_2\text{O}_3 \rightarrow \text{AlO}_2^- + 2\text{H}_2\text{O}$ , Al ions can be released into alkaline solutions by simple dissolution of the glass itself. Table 3 shows the amount of Al extracted from glass during steril-

isation of solutions of mono- and dibasic phosphates of potassium and sodium, sodium hydroxide, and bicarbonate and the pH of these solutions. It can be seen that the higher the pH, the higher the amount of Al extracted. Phosphate ions, that have themselves a high affinity for Al (see below), showed strong interaction only in solutions with alkaline character. Whereas both sodium and potassium monohydrogenphosphate solutions, with pH 10, extracted 1450 and 1550 µg/L Al respectively, the dihydrogenphosphate solutions, having pH 5, extracted only 200 µg/L Al.

Another possible way of withdrawing Al from glass is the also well known cation-exchange property of glass surfaces. When the action of different cations (chloride salts) is compared (Fig. 3b), it can be seen that it is not related to the pH, because the pH of all solutions was around or below 7. The effect could be due to a cation exchange process between glass and solution. All cations having an ionic radius similar to Al could be exchanged by Al. The strongest interaction occurred with chromium and copper ions, that have the smallest ionic radii among the investigated cations. The exchange of Al by Cr can be attributed not only to the size but also to a similarity between the ions. Both are highly-charged trivalent cations, that are easily hydrolysed in aqueous solution but remain unhydrolysed at low pH, and present an octahedral array of water molecules.

The third possible way of withdrawing Al from glass, and in this case as well from rubber, is through complex formation by action of ligands showing affinity for Al. According to the Pearson's theory of hard-soft-acid-base (HSAB) ligands (31), Al is a hard acid and therefore forms the most stable complexes with hard bases, e.g. phosphate ions ( $\text{PO}_4^{3-}$ ,  $\text{HPO}_4^{2-}$ ,  $\text{H}_2\text{PO}_4^-$ ) and other oxygen donor groups. As the HSAB theory indicates favourable combinations of these ligands and metal ions, it could explain the high affinity of Al for phosphate and gluconate ions. Besides this affinity, the pH also promoted the Al extraction by solutions of some phosphates, as already mentioned.

The effect of ligands could also be seen in solutions of complexing agents. The conditions (temperature and time of contact) having been similar, it is possible to relate the action of these substances to their affinity for Al. With an increasing stability constant of the Al complexes, the amount of Al released, either from glass or rubber, into the solution of the corresponding complexing agent increased too. The log *K* of the Al complexes are: EDTA

**Table 3.** Aluminium released into solutions of different anions during the sterilisation procedure.

| Anion                     | Cation | pH solution | Al released (µg/L) |
|---------------------------|--------|-------------|--------------------|
| $\text{OH}^-$             | Na     | 12          | 4300               |
| $\text{HCO}_3^{2-}$       | Na     | 9           | 1300               |
| $\text{HPO}_4^{2-}$       | K      | 10          | 1550               |
| $\text{HPO}_4^{2-}$       | Na     | 10          | 1450               |
| $\text{H}_2\text{PO}_4^-$ | K      | 5           | 210                |
| $\text{H}_2\text{PO}_4^-$ | Na     | 5           | 200                |

16.5, NTA 11.1, citric acid 7.9, malic acid 7.6 and oxalic acid 6.1 (32). The action of some amino acids could also be explained in this way, considering that their effect could not be caused by the pH of the solutions, which was not higher than 8.

Amino acids with polar side chains are able to form chelate complexes with metallic ions and extracted more Al from glass and rubber than pure water. In spite of the fact that stability constants of complexes between Al and the majority of amino acids are not known, the ability of amino acids to complex metal ions could be one of the reasons for the high Al contamination rates. In the literature, only the stability constants of Al complexes of aspartic and glutamic acids are listed. Cystine, on the other hand can be considered an exception: no metallic complexes with cystine are reported (32, 33), cystine showed, however, a high interaction with glass and rubber.

Among the other investigated substances albumin, heparin, glucose, mannitol, sorbitol and xylitol, there seems to exist an affinity for Al too. Albumin is a protein responsible for the unspecific transport of metals in the human circulatory system, therefore it should be able to form stable complexes with metallic cations. The other substances in this group have either -OH or -COOH groups. These oxygen donors can therefore act as basic ligands binding metallic cations such as Al.

## Conclusion

From the results obtained it can be concluded that, without other sources of Al in the industrial processing, the sterilisation of PN solutions by their heating in glass containers or in containers with rubber stoppers, may be mainly responsible for the presence of Al in these solutions. However, the Al release occurs only under certain conditions, e.g. an elevated pH, the presence in the solution of cations with similar properties to Al or ligands able to bind Al.

Solutions that meet these characteristics should be better stored in containers made of materials different from glass and rubber, or should not be submitted to a sterilisation process by heating, or otherwise should be stored in glass containers/containers with rubber closures that would not contain Al in their composition.

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