Report on the safety and efficieny of MANC® as the active ingredient of TOXAPREVENT® products

ABSORPTION AND REMOVAL OF ALUMINIUM AS WELL AS THE HEAVY METALS LEAD AND MERCURY

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Summary by Nouveau Health Ltd
Nouveau Health

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Content

1. Product Concept

1.1 Basic Knowledge on Clinoptilolite

1.1.1. Formation and Structure of Clinoptilolite

The structural formula and the composition of the raw material consists of a microporous structure made of aluminium and silicon atoms, connected by oxygen atoms. The ratio of silicon to aluminium in the clinoptilolite is 6:1-2. The tetrahedron is enriched with minerals such as calcium, potassium, sodium and magnesium. Depending on the structure type, the result of this configuration is a structure of uniform pores and/or channels in which substances are adsorbed.
Chemical formula: $(Ca, K_2, Na_2, Mg)_4Al_8Si_{40}O_{96} \times 24\ H_2O$

1.1.2. Functionality through Adsorption and Ion Exchange

Clinoptilolite's mechanism of action is based mainly on its ion exchange capacity. This is caused due to the electrostatic interactions based on the charge differences of the resident molecules. The silicon-aluminium-tetrahedron has an anionic charge structure in which cations in the form of calcium, magnesium, sodium or potassium settle. In the ion exchange process, the following components are removed as cations from the clinoptilolite and are replaced by other cations.
This is the replacement (output) of Ca^{2}+, Mg^{2+}, Na^{+} and K^{+}.

The adsorption is possible only in molecules which have a smaller kinetic diameter than the pores of the tetrahedron. Thus, the clinoptilolite has of a kind of a sieve function and therefore falls within the group of molecular sieves.

With the oral administration range of the products, the adsorption mechanism begins in the oral cavity/oesophagus/stomach (as is the case with the powder format of the product) or in the stomach/intestine (as is the case of the capsule format of the product).

Different elements (cations) are also adsorbed by ion exchange along the way through the digestive tract, depending on their location, in the order of selectivity.

Due to the selected middle particle size of 6 - 10 µm, the active substance passes through the human body in a purely physical way (without the metabolization).

Based on the in-vitro studies, the TOXAPREVENT® products bind the following substances:

- histamine
- ammonium
- heavy metals, such as lead and mercury
- light metal aluminium
- caesium
- as well as the following substances shown in Figure 1

Manc® – *in vitro* binding

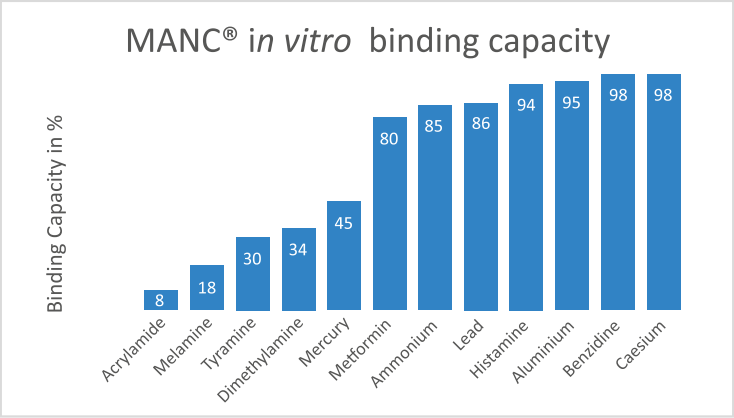

Figure 1: ion exchange capacity as the MANC's feature of performance

This functionality determines the intended purpose of the clinoptilolite products in the TOXAPREVENT® range. "Medical products for the detoxification of the digestive system and for relieving the liver."

1.2 Background of the Product's Development

Due to the current lifestyle and eating habits, people are permanently exposed to a wide range of substances. These are not immediately noticeable by the body's own regulation system but overstimulation or overstrain of the body's regulation system can cause its deviation from the natural path. This can often be caused as a result of the unnatural influences such as an unbalanced diet, an improper use of alcohol, tobacco, medication as well as various environmental influences.

The TOXAPREVENT® range of products can be used for prevention, treatment and therapy monitoring as well as to prevent the overload of the individual organs, due to its conversion functionality. This is achieved through adsorption of e.g. aluminium, lead and mercury as well as other substances. The mode of action of the TOXAPREVENT® range of products is purely physical because there is no metabolism in the body.

There are 4 variants in the TOXAPREVENT® ORAL range of products. These are PLUS, PURE, ACUTE & HALISTOP. They are available in capsules (PURE & ACUTE), chewable tablets HALISTOP) or powder form (PLUS). These products are all administered orally.
The main active ingredient is a micronized and activated natural calcium aluminium silicate (MANC®). For different therapeutic uses, different additive substances are used (see table 1.3 below).

This report intends to provide the proof of performance and harmlessness with regard to a possible metal exposure and to define the properties of the end products with respect to the functional features, especially with respect to the product safety assured to the user.

The conducted research took into account the current state of science and technology.

1.3 Product Description and Structure

The oral range of products are provided in the capsule and powder form to guarantee complete detoxification throughout the entire digestive tract because of the different intended reach of efficacy of the different formats (i.e. upper and lower part of the digestive tract).

	TOXAPREVENT® PURE	TOXAPREVENT® PLUS	TOXAPREVENT® PLUS	TOXAPREVENT® AKUT	TOXAPREVENT® HALISTOP
administration	capsule	capsule	powder	capsule	chewable tablet
packaging	blister	blister	stick	blister	blister
reach of efficacy	lower digestive tract (from pyloric orifice)	lower digestive tract (from pyloric orifice)	upper digestive tract (from mouth)	lower digestive tract (from pyloric orifice)	upper digestive tract (from mouth)
active ingredient	MANC®	MANC®	MANC®	MANC®	MANC®
addition		calcium carbonate magnesium carbonate	calcium carbonate magnesium carbonate	colostrum	Isomalt, lemon aroma, HPMC, magnesium stearate, stevia

2. Field of application: metals and metal intoxication

2.1. Aluminium

What is aluminium?

Aluminium is the most common metallic element, occurring in the earth's crust in a bound form. There are approximately 50 to 150 milligrams of aluminium in ionic form located in the human body. These are distributed approximately in the following way: 50 % on the lung tissue, 25 % on the soft parts and the remaining 25% on the bones. Aluminium is a natural ingredient of our body. It can be observed in the human microbiome too in the form of salts.

Causes for an increased aluminium load

Aluminium compounds find their way to the organism daily in small doses through food, alcohol, tobacco as well as environmental influences. The metabolism is carried out mainly by the kidneys. The danger of aluminium's concentration in the organism appears if the resorption barriers are being circumvented, or if the elimination through the relevant metabolic pathways is reduced or even stopped. This means: in case of acute infections or chronic diseases, the natural barrier between blood and tissue such as bone, brain or intestine can be broken, resulting in aluminium's concentration in the tissue.[1]

Occurrence[2]

Table 1: Occurrence of Aluminium and its compounds

native occurrence in food	additional sources
• raw plant food • seafood • offal • spices, chocolate • fermented raw products (tea, cocoa beans)	• food additives • food supplements • transfer from food contact materials • pharmaceuticals, cosmetics • work exposure in aluminium processing facilities

Symptoms [2]

The problem with aluminium is widely discussed. In cases of an overload of aluminium that cannot be fully metabolised by the kidneys and the bile, there is a risk of a toxic effect on the nervous system which is hazardous to health.

In the foreground of the analysis are mostly renal patients, especially those with the chronic renal insufficiency, in which the excretion functions insufficiently. According to the questions and answers about aluminium in food and consumer products, which the Federal Institute for Risk Assessment issued in February 2015, fertility, pregnancy and the bone development are also strongly connected to the toxicological effects of the metal due to its hazardous potential.

1 Informed Verlags AG, Beutler, Marianne, (28.04.1991), Aluminium toxicity, [online]. Available under: www.infomed.ch/pk_template.php, [13.04.2015]

2 The Federal Institute for Risk Assessment (BfR), Stähle, Sieglinde, (26.,27.11.2014), Aluminium in everyday life–a health risk? [online]. Available under: www.bfr.bund.de/cm/343/aluminium-im-alltag-ein-gesundheitliches-risiko-stellungnahme-der-lebensmittelwirtschaft.pdf, [13.04.2015]

Product testing by FROXIMUN AG regarding aluminium issue

In 2014 there was an occasion to identify the risk, in the context of the publicly controversial discussion on the possible health risks of aluminium as well as the diseases associated with it. The main focus of consideration was especially cutaneous and oral exposure sources. Since the raw material, "clinoptilolite, as used in the TOXAPREVENT® range of products contains aluminium-silicon compounds, the facts of the exposure to aluminium are recorded and evaluated for the user in the risk assessment of FROXIMUN® AG.

The overall aim of aluminium test is to determine whether there is a risk for aluminium resorption through the oral intake of the TOXAPREVENT® range of products. It should also be determined whether the adsorptive properties of the MANC® products give them the capability of binding and removing aluminium. The following data were obtained from *in vitro* and *in vivo* studies.

***In vitro* study to determine aluminium adsorption capacity of the MANC® in a neutral environment**

Test: Photometric determination of aluminium adsorption assets

Result: The quantitative determination showed that the MANC® is capable of binding different aluminium concentrations to virtually the same percentage of around 90 %. The results are reproducible.

Assessment: This could lead to the conclusion that in a neutral or alkaline environment, as it prevails in the gut, TOXAPREVENT® can absorb free aluminium salts.

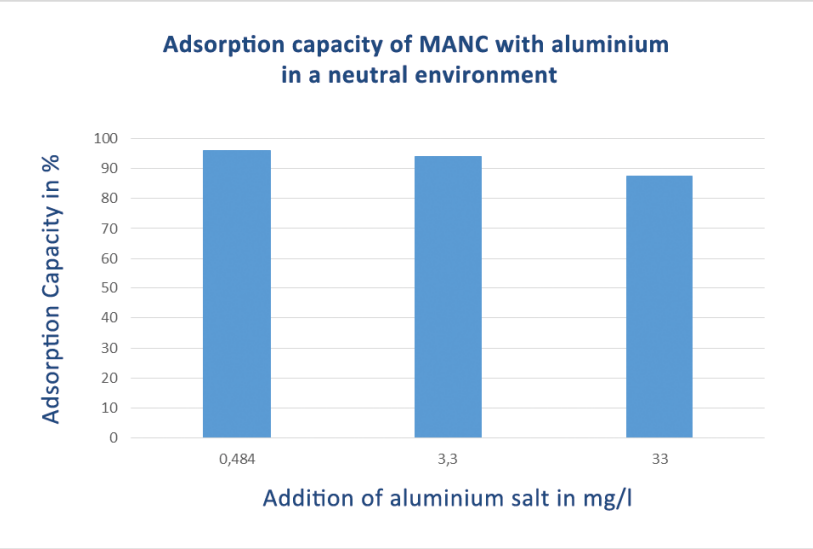

Figure 2: Adsorption capacity of MANC® with aluminium in a neutral environment

***In vitro* study to determine the response behaviour of the MANC® for aluminium in a synthesized digestive tract**

Test 1: Photometric determination of aluminium concentration at pH value change

Result 1: MANC® can react with stomach acids causing a release of the soluble aluminium salts.
In case of a pH value increase to the neutralization, the previously released aluminium salts are absorbed again, so that aluminium concentration is set below the limit of detection. The results are reproducible.

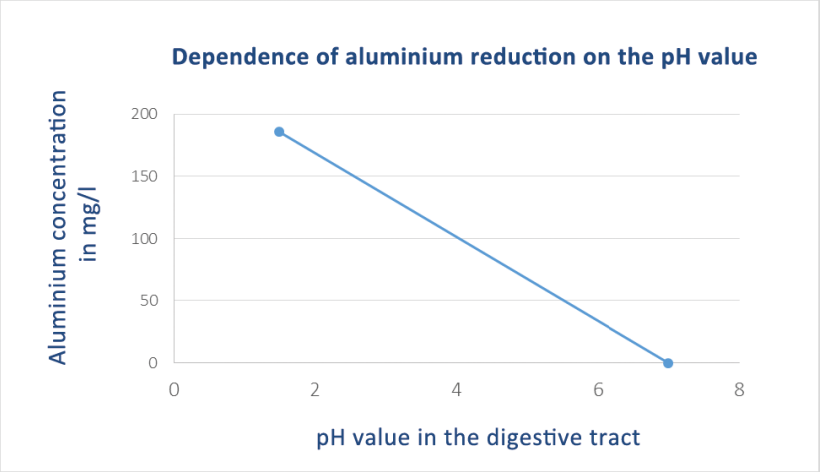

Figure 3: Dependence of aluminium reduction on the pH value with predefined aluminium concentration

Assessment 1: It is recognizable that the adsorption capacity increases with the increasing pH value.
If we transfer these facts to the human organism it can be concluded that when entering the duodenum, free aluminium salts are rebound immediately.

Result 2: The quantitative determination showed that the MANC® is capable of binding up to 87,17 % of the free aluminium salts in the digestive tract. The results are reproducible.

Assessment 2: Since before the entry into the absorption enabled area (gut) only small amounts of aluminium were detectable, it can be assumed that TOXAPREVENT® containing the active ingredient MANC® can be used for aluminium binding and metabolism.

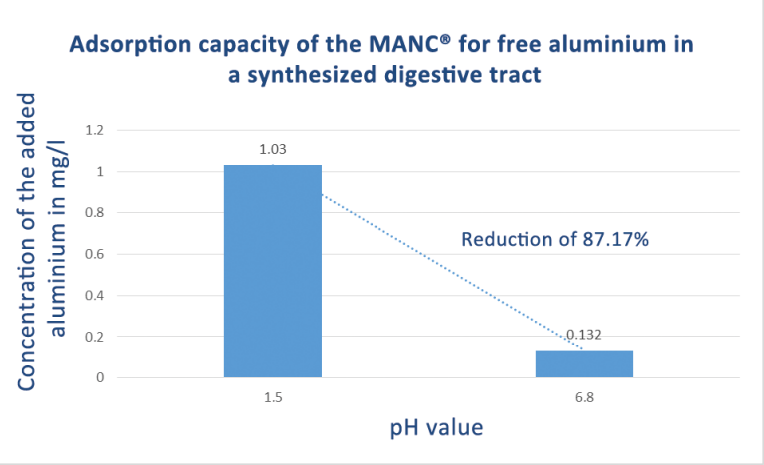

Figure 4: Adsorption capacity of the MANC® for free aluminium in a synthesized digestive tract

Clinical data to demonstrate safety of the product regarding aluminium exposure through the application of MANC® as an active ingredient of TOXAPREVENT® range of products.

Aim: Detection and exclusion of the potential risks for long-term users of the medical range of products FROXIMUN® by possible hazardous storage of aluminium.

Test: Determination of aluminium's concentration in 21 persons on the basis of a blood test. The dose administered daily per person was more than 2 grams of the MANC®.

Result: For 15 subjects, the value was < 3.0 µg/l, i.e. below the limit of detection (here 3 µg/l).
For 6 subjects, the value was between 3.9 and 7.7 µg/l, i.e. above the detection limit and far in the lower reference range.

Assessment 1: On the basis of the low or no aluminium concentrations in the blood of the participants, it can be assumed that there is no over-concentration and storage of aluminium.

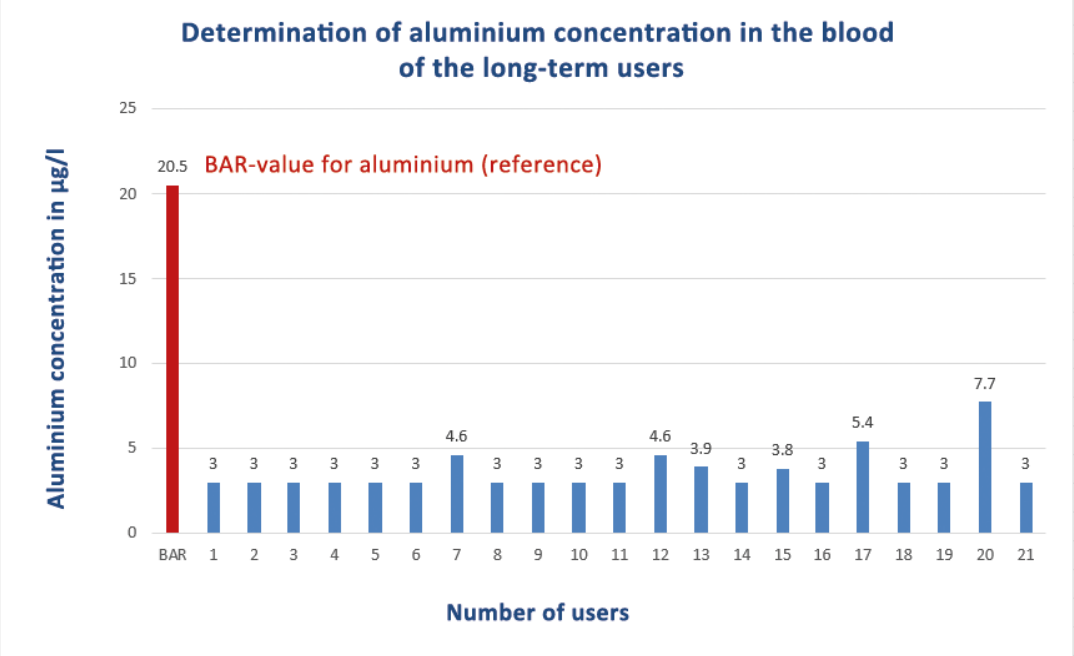

Figure 5: Determination of aluminium concentration in the blood of the long-term users of TOXAPREVENT® for oral application

Test report on the examination of the long-term application of natural zeolite: aluminium silicate for the verification of the possible accumulations of aluminium in the human body and possible pathological consequences (data gained through literature)

Scope of the test: 11 persons with long-term use of clinoptilolite, 12 persons without the use of clinoptilolite as a control group

Test: Determination of aluminium, iron: Mass spectrometry with inductively coupled plasma

Results:

Hair values: In Table 2 it can be seen that no aluminium has stored up over the period of long-term application.

Blood values: On the basis of aluminium concentration in tab. 2 it is recognizable that the values of the long-term users are below the reference value. A surplus of aluminium in the blood could not be proven in any user.

Urine values: Five people secreted a surplus of aluminium with the urine.

Subject no.	1	2	3	4	5	6	7	8	9	10	11
sex	F	F	F	M	M	M	M	M	M	M	F
Duration of the zeolite-taking in years	11	6	2	6	13	3	2	2	2	2	2
aluminium in the hair < 17.3 µg/g	-	1.9	3.0	2.2	1.0	2.8	0.9	2.6	6.4	4.8	5.5
aluminium in the blood < 10.0 µg/l	3.0	5.0	7.0	5.0	7.0	5.0	5.0	5.0	5.0	4.0	3.0
aluminium in the urine < 22.3 µg/g	24.6	29.8	16.4	63.3	41.9	2.5	61.7	10.7	1.5	9.8	4.8

Table 2: data for the long-term application of clinoptilolite-zeolite

Subject no.	1	2	3	4	5	6	7	8	9	10	11	12
sex	M	M	F	F	M	F	F	F	F	F	F	F
Duration of the zeolite-taking in years	-	-	-	-	-	-	-	-	-	-	-	-
aluminium in the hair < 17.3 µg/g	3.6	5.8	-	3.8	0.7	-	23.4	-	2.3	1.0	2.0	2.0
aluminium in the blood < 10.0 µg/l	3.0	72.0	< 3.0	< 3.0	< 3.0	< 3.0	< 3.0	< 3.0	< 3.0	< 3.0	< 3.0	< 3.0
aluminium in the urine < 22.3 µg/g	6.4	9.8	9.1	5.1	7.5	7.4	0	0	4.6	2.6	0	7.5

Table 3: data of the control group

Assessment: When comparing the data in the long-term users with the control group, no conspicuous difference except for the urine test can be detected. Background of the excessive aluminium excretion via urine could lie in the fact that the affected subjects (1, 2, 4, 5 and 7) drink at least 3 cups of black tea per day, which according to the BfR (Schäfer [2015]) can be a source of exposure to aluminium, but within 24 hours this aluminium is excreted again and there is no load of it in the organism. The iron values are in the optimum too, what should be noted as a positive fact, as aluminium and iron are closely linked with regard to their proof analysis in the blood.

For the enteric resorption, aluminium uses the same transport system as iron and can displace it in the tissues from its functional connections. Therefore, in case of a heightened concentration in the tissue, an iron deficiency would occur, which however was not the case. On the basis of the data available in the table 2 it can be assumed that the storage of aluminium in the organism doesn't occur as a result of the ingestion of clinoptilolite.

Report of experience in the application of TOXAPREVENT® in patients with immune deficiency syndrome (IDS) and amyotrophic lateral sclerosis (ALS)

Scope of the test: 16 persons

Test: Implementation of *in vivo* testing to detect aluminium reduction in the human organism

Reference values: Aluminium in plasma: < 7.5 µg/l Aluminium in serum: < 10 µg/l
From 10 to 60 µg/l = increased aluminium values
From 60 to 100 µg/l = monitoring is required
From > 180 µg/l = osteodystrophy is assumed
From > 200 µg/l in plasma = clinical symptoms of encephalopathy must be considered.

Result: In 6 of 6 IDS-patients aluminium was removed from the blood cells after the application of TOXAPREVENT®.
In 10 of the 10 ALS patients no aluminium in the blood could be proven after the application of TOXAPREVENT®

Assessment: Due to the collected lab results, it can be seen that the use of TOXAPREVENT® causes the reduction of the elevated aluminium levels and no increase. It can therefore be assumed that the resorption of aluminium didn't occur as a result of the oral application of TOXAPREVENT®. This creates a great benefit in terms of the controversial toxicology of the element. The process of concentration reduction can be explained on the basis of the afore mentioned *in vitro* studies. Due to the collected lab results, it can be seen that the use of TOXAPREVENT® can be successfully used for the reduction of the elevated aluminium levels.

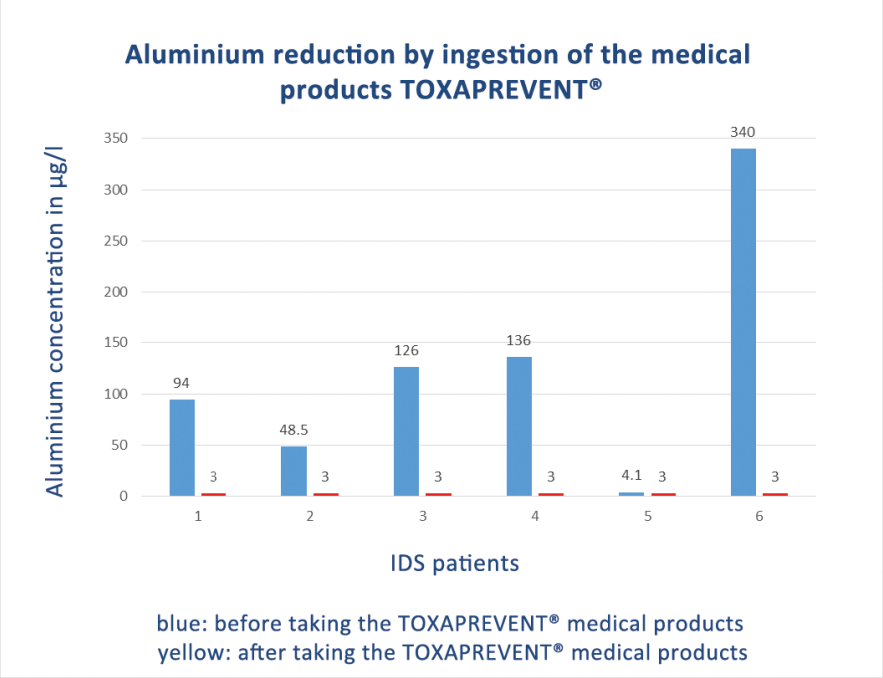

Figure 6: aluminium reduction by intake of TOXAPREVENT® in IDS patients

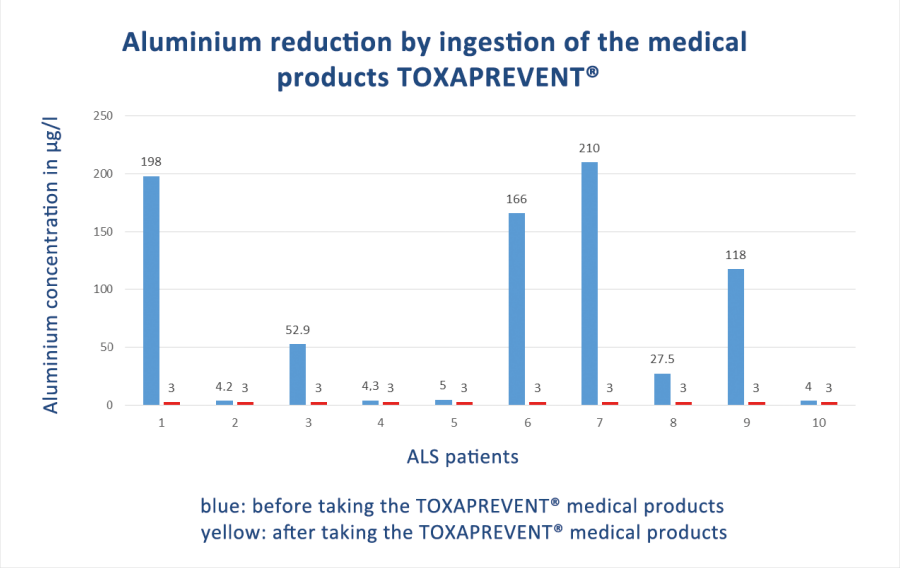

Figure 7: Aluminium reduction by intake of TOXAPREVENT® in ALS patients

Conclusion

The tests are systematically coordinated and show in their different approaches which possibilities of aluminium exposure can occur.

Firstly, the active substance - aluminium silicate - and thus the source of a potential exposure to aluminium was checked. Here it is clear that the MANC® can react without further influential factors in the strongly acidic conditions involving the release of soluble aluminium salts. However, if the MANC® is located in a neutral environment, no aluminium is dissociated.

In a further experiment, the products' natural pathway through the digestive system was simulated. However, here only the active substance MANC® is considered, and not the products MEDI PLUS or HALISTOP®. In the stomach environment (pH=1.5) aluminium is released under given circumstances, but with the nearly neutral pH value, as in the duodenum, it is absorbed again to 100% and is no longer detectable. The change in pH value by the supply of alkaline secretion occur in the digestive tract (transition between stomach and intestinal tract) with an immediate effect as soon as the acid chymus comes into contact with the intestinal mucosa.

This meant that before the mixture of the MANC® and aluminium salts was present in the absorption enabled part of the digestive system, a complete adsorption of the existing aluminium took place and there was more capacity to absorb free exogenous aluminium compounds.

What has been done by FROXIMUN AG in the context of a risk-benefit analysis?

The conducted tests provide a reasonable basis for the assumption that the oral intake of TOXAPREVENT® does not cause aluminium release in the body, but the absorption of its different higher concentrations in the intestinal tract. To eliminate a possible remaining risk, additional risk control measures were carried out:

- **Use of the gastro-resistant capsules, made of safe ingredients that may be used in quantum satis.**

In this way the interaction of the MANC® with stomach acid is bypassed, which completely prevents the dissolve of aluminium components. Thus the possible release due to the delivery of TOXAPREVENT® PURE, PLUS and ACUTE in the capsule form is excluded.

- **Adding the ingredients with higher pH values, such as calcium and magnesium carbonate to the MANC®**

Addition of calcium and magnesium carbonate to the MEDI PLUS Sachets, so that through the mixing of the powder with water a higher pH value of approx. 7.5 - 8 sets in. As a consequence, **the product applied on an empty stomach** is not entirely reduced to the strongly acidic pH value of 1.5, but attains a weak acid or an almost neutral pH value of 5.5 to 7. The release is thus reduced or completely prevented. Since the product, according to the directions for use, must be taken before a meal, the pH value increase has no influence on the digestion or decomposition of the chymus, since this is not simultaneously as the product in the stomach. The digestive processes are therefore not influenced. The same applies to the **TOXAPREVENT® HALISTOP® chewable tablets.**

In the further observations it was examined how the MANC® reacts in a neutral environment regarding the added aluminium.

The results of the experiment showed a strong adsorption capacity of up to 95.9%. The attempt shown on Figure 4 reinforces this finding, as the adsorption capacity of the MANC® was tested after it passed completely through the stomach and transited into the intestinal tract.
Here too the MANC® has, despite prior pH value load, a strong affinity to freely available aluminium salts and causes a reduction of this concentration of up to 87,17 %. The results of the *in vitro* studies reflect the results of the *in vivo* studies; it can be spoken here about a product with a minimal risk (application error), but with a great benefit.

Benefits - summary on aluminium binding

The use of elements adsorption has beneficial results in many ways. On the one hand, TOXAPREVENT® can be taken preventively by the end-users of aluminium-containing food, cosmetic articles or other products to prevent an aluminium intoxication.
On the other hand, the medical products TOXAPREVENT® can and will be used in the course of the occupational health management at the exposed working places for health maintenance.

2.2. Heavy metals - lead and mercury

What are heavy metals?

Heavy metals are substances occurring as various compounds, coming from nature or from the industrial environment. Some of these heavy metals are essential in small quantities for flora, fauna and people, while others in the same concentration can already have toxic effects. The way through the various branches of industry, industrial processing or through the natural erosion in the environment varies.

What can heavy metals cause?

Increased lead and mercury concentrations in the human organism can cause serious as well as chronic diseases. The symptoms are often not connected with a heavy-metal pollution and the cause is not eliminated.

Lead

Causes of lead pollution

Lead and lead compounds appear i.a. as a residuum or direct processing resources in the products of daily use. Overloaded systems are for example:

- air, water, ground,
- plants, animals,
- food,
- drugs, everyday products and food contact materials

They are therefore not only an integral part of the food chain, but became a general risk factor through the daily contact.

Lead - instead of calcium- accumulates in the bone tissue and is excreted very slowly from it. (cf. the Federal Institute for Risk Assessment, www.bfr.bund.de/de/search.html, "Heavy metals")

Symptoms of lead pollution

According to the Federal Institute for Risk Assessment, already the small doses (mg) of lead cause severe chronic poisoning if the organism is exposed to them for weeks or months. They can be absorbed via the food, the drinking water, over the air by inhalation or through the skin. If it happens over a longer period of time, it can lead to a chronic poisoning.

Following are possible consequences:

- kidney damage
- paralysis in the limbs
- brain damage, such as epilepsy-like spasms
- damage to the nervous system
- cardiovascular malfunction
- stillborn and sterility
- gastrointestinal disorders

Since July 2006, the German Research Foundation (DFG) assesses lead and its inorganic compounds as "carcinogenic in animal experiments". Lead poisoning is recognized as an occupational disease under the BG-Code 1101.

Mercury

Causes of mercury pollution

A mercury pollution can have various causes. It can get into our organisms from different sources. It is released into the environment by the different industry sectors and is deposited in the soil and water. There it is partly transformed into methyl mercury, which can be found in large quantities in the sea animals. Therefore, food, among other things, is classified as one of the main contaminants and causes of a mercury load. Also the use of objects such as energy-saving lamps, whose break causes mercury to be absorbed via the lungs as vapor, can cause health damage. In the dental medicine, the use of amalgam is controversially discussed, as it is a further cause of chronic mercury poisoning. In the past, partially also vaccines included high concentrations of mercury compounds.

Symptoms of mercury pollution:

In the case of a chronic poisoning, mercury is stored in the organism. Increased concentrations are then deposited in teeth (pine, root, teeth), spleen, kidneys, brain and spinal cord as well as in nerve tracts and are only slowly excreted via kidneys.

Symptoms of a chronic mercury poisoning:

- Effects on the entire system:
  - o chronic headache
  - o allergies
  - o abnormal body temperature
  - o chronic kidney disease
  - o general fatigue

- Head, neck, throat area:
  - o gum bleeding, tooth loss, increased salivation,
  - o metal taste, mucositis, ulcers
  - o dizziness, voice, visual and hearing disorders

- Gastro-intestinal system:
  - o food intolerances,
  - o abdominal cramps, colitis,
  - o gastrointestinal disorders,
  - o chronic diarrhoea, constipation

- Heart and vascular disorders:
  - o abnormal heart rhythm
  - o abnormal blood pressure

- Immune system:
  - o autoimmune disorders
  - o repeated infections
- Later the signs of damage to the nervous system may occur:
  - o nervousness, excitation and anxiety states
  - o restlessness, mood swings
  - o numbness/tingling in the limbs

***In vitro* evidence for the binding of lead in a synthesized digestive tract by the MANC®**

Test: Determination of adsorption assets using the optical emission spectrometry with inductively coupled plasma

Result: The tests show that at the pH 1.5 a significant absorption of lead takes place. With 0.5 g of the MANC®, 32 % of the provided lead is absorbed. At the pH = 8,1 and with 0.5 g of the MANC®, 86% of the provided lead is absorbed.

Assessment: It is recognizable that the active substance MANC® has a strong affinity to lead and can be used for the reduction of this substance.

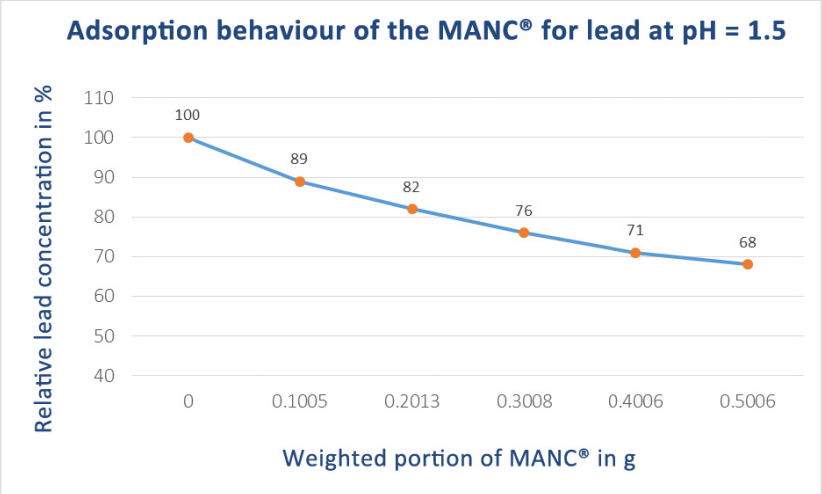

Figure 8: The Adsorption behaviour of the MANC® for lead at pH = 1.5

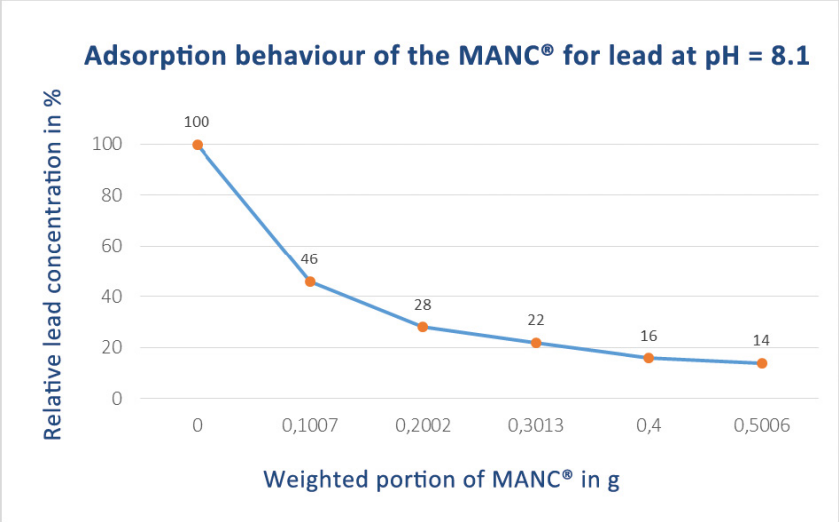

Figure 9: The Adsorption behaviour of the MANC® for lead at pH = 8.1

***In vitro* evidence for the binding of mercury in a synthesized digestive tract by the MANC®**

Test: Determination of the adsorption assets by cold vapour atomic absorption spectrometry

Result: The tests show a good absorption of mercury at pH 1.5. With 0.5 g of the MANC®, 57 % of the provided mercury is absorbed. At pH 8.1 and with 0.5g of the MANC®, 45 % of mercury is adsorbed.

Assessment: It is recognizable that the active substance MANC® has a strong mercury affinity and can be used to reduce the substance.

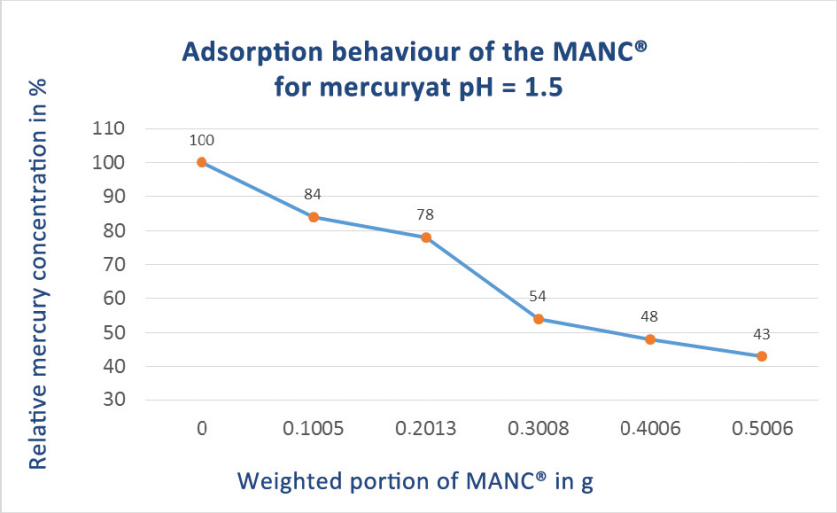

Figure 10: The Adsorption behaviour of the MANC® for mercury at pH = 1.5

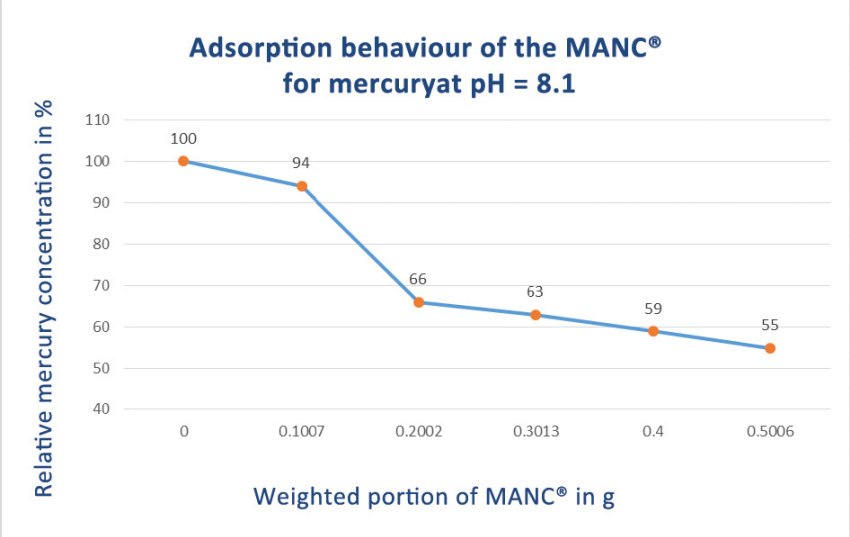

Figure 11: The Adsorption behaviour of the MANC® for mercury at pH = 8.1

Clinical data to demonstrate the safety of the product for the heavy metal exposure, on the basis of the natural deposition

Natural heavy metal deposition, such as of lead and mercury, which are present in almost every natural zeolite, were also examined. Due to the absorption capacity of the MANC®, the above mentioned heavy metals are bounded. Despite these proven quality, on the basis of studies for long-term application of the medical products TOXAPREVENT® it has been examined whether the chemically simulated *in vitro* studies can be validated.

Goal: The exclusion of the release and absorption of the natural heavy metals deposition, using a data collection that demonstrates that the active substance MANC® doesn't cause the harmful concentrations of heavy metals even with long time use on humans and that the previously collected *in vitro* data are credible.

Method: Conducting a routine examination in the context of occupational health management of FROXIMUN® AG, whereby the persons considered for the examination had been daily taking more than 2 grams of the MANC® for over 60 months.

Test: The determination of the heavy metals concentration for lead and mercury on 21 persons with the use of a blood test.

Result: The investigation showed an extremely low concentration of lead and mercury in the blood of the participating persons compared with the usual average reference values. The results show that the users of oral application forms of TOXAPREVENT® series are not exposed to any health burden. The products can be classified as harmless and biocompatible for humans.

Mercury: 6 persons were below the detection limit of < 0.1 µg/l.
14 persons were above the detection limit in the lower tolerance range.
1 person (5 amalgam fillings) amounted to 2.6 µg/l slightly above the reference value.
20 of 21 persons were below the BAR reference value.

Lead: 10 of 11 women were below the BAR-value of < 70 µg/l
1 woman was above the normal reference range (74 µg/l)
10 of 10 men were significantly below the BAR-value of 90 µg/l

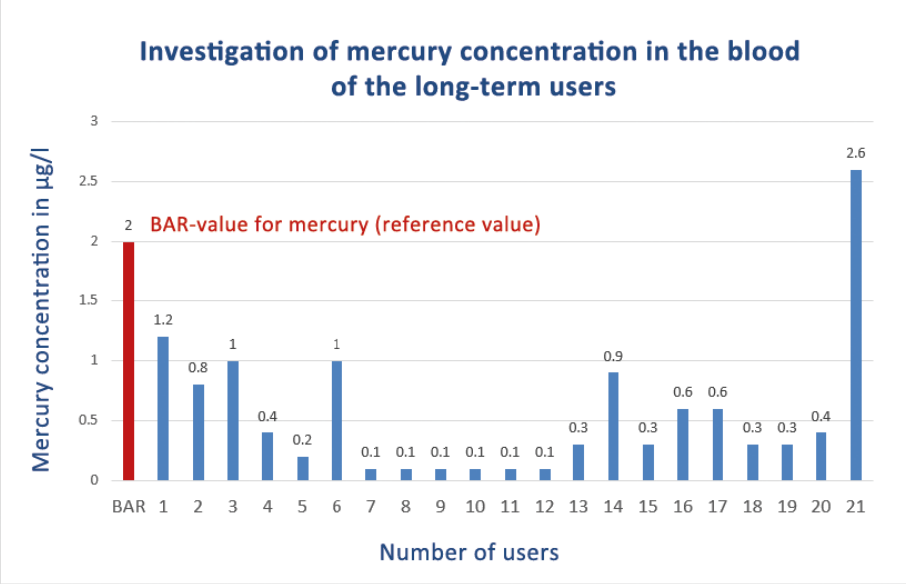

Figure 12: Investigation of mercury concentration in the blood of long-term users

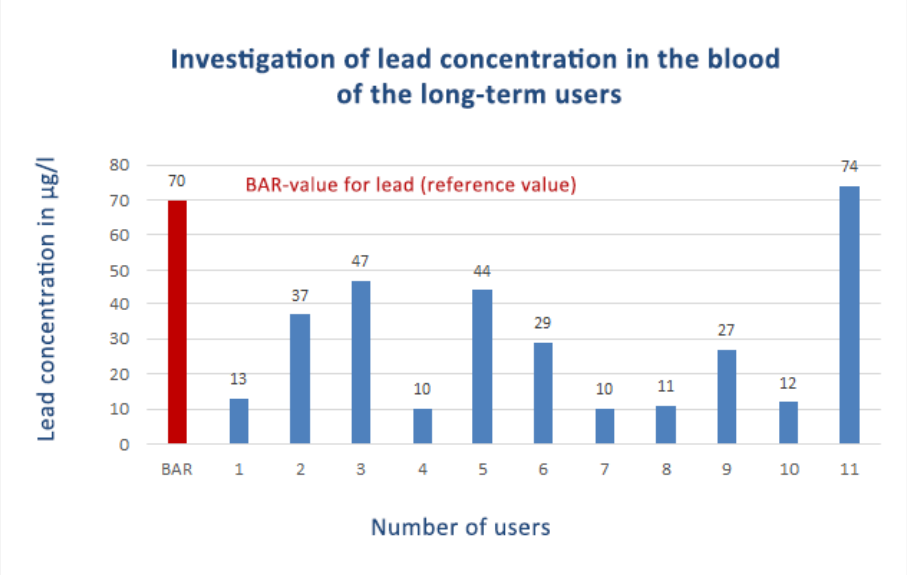

Figure 13: Investigation of lead concentration in the blood of the long-term users

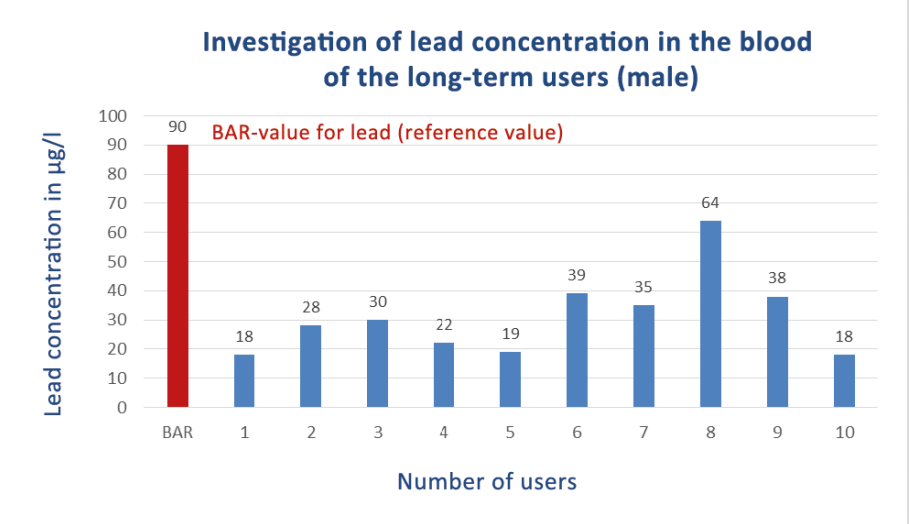

Figure 14: Investigation of lead concentration in the blood of the long-term users (males)

Assessment: On the basis of the above presented data it is clear that there is a reduction of lead and mercury in the digestive tract, both in the stomach and the intestine. Hence, the *in vitro* results can be transferred also on the human organism. Thanks to the *in vivo* studies it could be determined, on the basis of the above mentioned blood investigation, that no heavy metals deposition was present as a result of the oral use of the medical products.

Benefits - summary on heavy metals binding

The use of elements adsorption has various beneficial effects. On the one hand, TOXAPREVENT® can be taken preventively by the end-users of the lead-containing food, cosmetic articles or other products to prevent a lead intoxication. On the other hand, the medical products can be used in exposed workplaces, e.g. in the heavy metal processing industry. Here the products can be integrated into the company's health management, to offer the employees the opportunity to receive measures for health maintenance as a heavy metal reduction measures. This includes also dentists that deal with the amalgam removal.

3. Risk-benefit evaluation

3.1. Risk evaluation

After evaluation of the conducted tests and trials in which *in vitro* and *in vivo* results go hand in hand and confirm each other, no biological hazard for the human organism can be found in the active substance MANC® and the medical products developed from it. The products have a good biocompatibility. There is no health risk for the user. The test for the acute systemic toxicity also showed that there is no danger from the product itself. Also the test for the irritations and skin sensitization showed that the products do not cause irritation to the skin, no sensitization and no irritation of the oral mucosa. On the basis of achieved sensitization awareness rate of 0-8%, the products have been classified in the allergy class 1. It is a safe raw material. Due to the constantly updated risk monitoring system which is especially focused on the possibly detachable components, the long-term users were examined after a minimum of 5 years of use to assess any actual changes or additions in the body that could be caused by taking TOXAPREVENT®. The *in vivo* results confirmed that TOXAPREVENT® are safe medical products. This is supported by over ten years long product experience of doctors, therapists and scientists, who confirm the safety and functionality by administering the product on a daily basis to the patients and users.

3.2. Benefit evaluation

According to the current data, the benefits coming from taking the orally administered products in regard to the therapeutic and preventive application for reduction of aluminium and the above mentioned heavy metals to body detoxification and to relieving the liver are neither weakened, nor mitigated by any resulting risk. The risk-benefit ratio can only be considered as more beneficial than risky. More benefits of the products, verifiable by the clinical use, have been confirmed in the conducted tests. Especially the clinical data on aluminium reduction in the organism show the benefits for the user. This means that a therapeutic and preventive measure for the reduction of an over-concentration of aluminium in the body can be provided through the detected adsorption ability. The newly asserted benefit would be useful in regard to the protection in the workplace, as the TOXAPREVENT® could be made available for aluminium and heavy metal extraction for employees in exposed workplaces. Chronic or acute metal intoxication could be treated with TOXAPREVENT®

4. Conclusion

In vivo and *in vitro* data presented here show straightforwardly the current state of knowledge and the harmlessness of the elements of exposure. In spite of some questionable causal relationships between aluminium and diseases associated with it, the product testing is essential to provide the user with a secure and harmless product with high benefits.

The clinical data quantitatively provide a stable basis to convey meaningful information and to make qualitatively justified statements. Different methods were selected for data collection. Here the *in vitro* studies and clinical data have been used. Studies conducted on 48 previously described human individuals proved that there is no increased aluminium concentration in the body, either temporarily or for long periods of time. The risk-benefit analysis allows therefore FROXIMUN® AG to issue a strong safety statement.

After the evaluation of the available data, it can be said that the medical products in the Toxaprevent® range have a high value and benefit and low risk. It is not only the assessed case studies that confirm this benefit of aluminium adsorption as well as adsorption of the heavy metals lead and mercury. The fact that the Toxaprevent® range of products have already been used repeatedly, without negative feedback, several million times in Germany alone for this purpose also confirms the benefits. In no cases was there a reference to a possible additional aluminium load or heavy metal intoxication. On the basis of this evaluation, it can be noted that the tested medical products from FROXIMUN® AG pose no danger, but have a high therapeutic use.

Ellen Görner, B.Sc. (QAR)
Safety representative of the FROXIMUN® AG