CE 0197
medical device

- Certified Management System
- EN ISO 9001
- EN ISO 13485

PANACEO med
Activated Zeolite

SCIENTIFIC SUMMARY

An evaluation of the current knowledge concerning natural zeolite clinoptilolite in respect to application on humans based on published studies, clinical observations and field reports.

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1. INTRODUCTION

This work lists, analyses and critically evaluates, literature considered relevant to Panaceo medical products. The work includes all relevant areas on the topic zeolite from the history, over the toxicological knowledge, the effectiveness, to the possibilities of use.

1.1. Basics and comparability of results

An overview of the uses and basic research on the main substance clinoptolite is given in Mumpton [30], Armbruster [12] und Hecht [41], see also the chapter the 250 Year History of the Natural Zeolite, Clinoptolite“. The “irregularities” in natural clinoptolite described by Armbruster only have a quantitative effect on the ion exchange. This does not affect the characteristic selectivity alignment. This means that it can be assumed that the use of the zeolite containing 84% clinoptolite specified in the data sheet can be compared to other studies with a corresponding amount of clinoptolite. Small quantitative deviations are unavoidable anyway in a natural substance.

The **natural zeolite clinoptilolite** used in Panaceo products has the following technical specifications:

1.2. Technical specifications - Clinoptilolite

Characteristics of the raw material Macroscopic zeolite, a compact rock, light green in colour (moist) with a mussel-like section**.** Dry material is light grey in colour.
Specific weight: 2200-2440 kg/m3.
Dimensional weight: 1385-1905 kg/m3
Water absorption capacity: 39 %
Porosity: 24 – 32 %
Partial exchange capacity NH4: 0,7 mól/kg
Total exchange capacity NH4: 1,3 mól/kg
Chemical composition:

SiO_2	64,18-75,50%	Al_2O_3	10,93-14,80%	MgO	0,29-1,43%	K_2O	1,24-4,24%
Fe_2O_3	0,12-2,45%	CaO	1,43-11,68%	Na_2O	0,10-2,97%		

Mineralogical composition :

Clinoptilolite – 82 – 84 %
Cristobalite - 9 %
Feldspar - 5 – 8 %
Mica - 2 –3 %
QQuartz - trace

Fig.1: Zeolite

1.3. 250 Year History of Natural Zeolite Clinoptilolite

The natural mineral zeolite was first described in 1756 by the Swedish researcher Axel A. F.

The clinoptilolite, also called heulandite, a sub-group of zeolite, belongs to the crystalline zeolite forms. There are world wide more than 100 different zeolite forms, along with the crystalline also phase-like and petalled. There are 40 different types of natural zeolites, of which especially heulandite-clinoptilolite and mordenite are used for their ion exchange capability and adsorption properties.

Zeolites have the ability to adsorb the molecules of appropriate cross-sectional diameter (adsorption property, or acting as molecular sieves) and to exchange their constituent cations without major change of their structure (ion-exchange property) [133, 134]. The exploitation of these properties underlines the use of zeolites in a wide range of industrial and agricultural applications and particularly in animal nutrition since mid-1960s [30].

The basic frame of clinoptilolite-zeolite is a crystal grid and displays a homogeneous hollow space of 4 Angstroem. The crystal framework consists of silicon (SiO_4) und aluminium (AlO_4) tetrahedral. In these close net-like crystal grids there are cations like calcium, magnesium, sodium, potassium etc. [41]. The effectiveness of the adsorption depends greatly on the silicon-aluminium relationship of the raw material. Raw materials with a similar Si/Al relationship therefore have similar properties and comparable effectiveness. In addition the zeolites are more acid stable the more silicon and the less aluminium portion in the mineral [120]. The Panaceo clinoptilolite has 65-75% SiO_2 compared to approx. 11-15% Al_2O_3 a high portion of silicon [120] and therefore a high acidic stability. In addition zeolites are also characterised by their high proportion of internal surface that has in the rule an approximate size of 300-700 m^2/g [120].

At a very early stage the selective adsorption capability and in connection with that the molecular sieve was discovered and put to industrial use. Clinoptilolite is used especially in industry to clean nuclear, urban and industrial effluents [43], to clean industrial exhaust gas and to produce high purity oxygen (95%) [59, 60, 61]. The use of zeolites in agriculture to control fertilizers, pesticides, herbicides and moisture storage is wide spread. Natural zeolites are also used in pet food and to remove ammonium from pet food and in aquaculture. Since 1969 zeolite has been used for cooling, freezing and solar energy and other heat sources [59, 62, 63, 64, 65].

Since 1965, experiments have been in progress in Japan on the use of natural zeolites as dietary supplements for poultry, swine and cattle. Based on the successful use of montmorillonite clay in slowing down the passage of nutrients in the digestive system of chickens and the resultant improvement in caloric efficiency, as reported by [235]), clinoptilolite and mordenite have been added to the normal protein diets of pigs, chickens, and ruminants at several agricultural stations and livestock farms in Japan. Significant increases in the gain of body weight per unit of feed consumed (feed efficiency) and in the "general health" of the animals have been achieved [236]. [234]

The first international conference on the occurrence and possibilities of use of natural zeolite was organised in 1976 by Fred A. Mumpton and L.B. Sand in Tucson, Arizona.

Clinoptilolite is the most used natural zeolite. Already in 1997 more than 3.6 million tons of clinoptilolite were produced world wide [80] whereby the main areas of use are cat litter, pet food, fertilizer and ecological absorbents [12]. After the Chernobyl disaster in 1986 a total of 500,000 t of zeolite, mainly clinoptilolite, was used partly in the sarcophagus [12,81], partly in the water purification - whereby a drastic reduction in radio activity was registered [82,83], some more on water purification, esp. the Dnieper river and the effluent of the nuclear energy plant. The filtration reduced the water contamination from ^{137}Cs by 95%, ^{90}Sr by 50-60%.[82]. Finally to reduce the concentration

of Cs in cow milk 10% clinoptilolite was mixed into the cow fodder, which leads to a reduction of 30% of Cs in the cow milk [84]. To decontaminate children from Cs2-30 volume percent of pure powder clinoptilolite was added to chocolate and biscuits [84].

Also aflatoxin concentration in milk could be reduced by the addition of clinoptilolite to the fodder. Pigs, chickens and turkeys can be protected against aflatoxin by an additive of clinoptilolite in the contaminated grain. It was determined that an improved growth and nutritional exploitation in general and a reduction and easing of diarrhoea in particular of pigs, cows, sheep and chickens could be achieved with the admixture of clinoptilolite in fodder [12].

Many researchers have proved that the dietary inclusion of zeolites improves average daily gain and/or feed conversion in pigs, calves, sheep and broilers [135]. Zeolites also enhance the reproductive performance of sows, increase the milk yield of dairy cows, and the egg production of laying hens and have the beneficial effects on egg weight and the interior egg characteristics [135].

Promoting properties of the dietary use of zeolites in animals included:
- elimination of toxic effect of NH4+ produced by intestinal microbial activity [137, 138],
- reduction of the absorption of toxic products of intestinal microbial degradation, such as p-cresol (139),
- slower passage rate of digester through the intestines and more efficient use of nutrients [140, 141, 142],
- enhanced pancreatic enzymes activity through the favourable effect on feed components hydrolysis over a wider range of pH, improved energy and protein retention [143, 144],
- aflatoxin sequestering effect [145, 146].

1.4. Worldwide Registration

Calcium aluminium silicate is registered in the EU as the additive E 556. Clinoptilolite is registered for animals under the regulation no. 739/2000.

In the USA the FDA classifies the substance as generally safe in the " Code of Federal Regulations, Foods and Drugs (FDA), 21 CFR CH.I, §182 Subpart C "

In Japan in the „Specifications and Standards for Foods, Food Additives, etc. Under The Food Sanitation Law" zeolite has been registered as a food additive since April 16.th 1996 and has been used there for different types of animals since 1965.

2. NATURAL ZEOLITE CLINOPTILOLITE: SAFETY, DANGERS, RISKS?

Since the supplementary oral administration of clinoptilolite to humans has already been taking place for more than 20 years (see Chernobyl disaster 1986) long-term experience in handling the application of clinoptilolite to humans per oral can well be assumed. In the case of Panaceo in addition to pre-clinical, clinical studies and practical use also wide experience regarding possible side effects can be referred to.

The specifications of the raw material from the manufacturer were verified by x-ray diffractometeric tests. The results proved that the raw material contains between 85-90% heulandite-clinoptilolite as specified by the manufacturer. The thermal test at 350 degrees C led to no change in the diffractogram. There were no significant amounts of natrolite. Admixtures of phonolithic rock mineral could not be proven.

2.1. Stability

Natural zeolite clinoptilolite displays a high thermal stability and resistance to aggressive substances, especially to acids and ionising rays [45,46,47,46]. No effects detrimental to health were determined in human or animal organisms by long-term application [41, S260]. 260]. In an experiment by Patzer et al in 1995 on the absorption of ammoniac by natural clinoptilolite no release of silicon or aluminium particles was detected [24]. In an experiment by Eugenio et al (1995) after a single dose of 3.36 and 0.90 mg/kg of Na-Aluminium-silicate and also the other aluminium compounds used showed no statistically significant increase in the blood plasma level measured over 24 hours. Also the publications mentioned during the experiments on ammonium absorption gave no indication of a strain due to the aluminium proportion [24].

In experiments on the behaviour of clinoptilolite in stomach acid (PH 1.2, 2wt% zeolite powder) over 48 hours no dissolved aluminium was found [90].

In the gastrointestinal sector clinoptilolite remains stable [12]. Already in 1989 an experiment by Pond et al confirmed the stability of clinoptilolite in the gastro-intestinal area of pigs [100].

In addition to the calcium aluminium silicate E 556 there are several other chemically related additives that are registered containing aluminium. The possible traces of heavy metals present in the raw material are on the one hand measured in the analysis of the raw material and therefore minimised in the forefront during the selection of the raw material and on the other, present no risk as they are bonded anyway by the natural zeolite clinoptilolite and are not released. [cp. chapter " Bonding and release of heavy metals, ammonium and radioactive cations"].

There is some concern about the possibility of zeolite dissolution or degradation during use, which could lead to solubilization or particulate colloidal suspensions containing Si or Al, the major building blocks of zeolites. Patzer et al. [225] analyzed the final effluents from each ion exchange run for the presence of Si and Al using atomic absorption spectroscopy. They detected neither within the limits of detection of the instrument (1 part per million) [226].

Clinoptilolite is resistant to degradation by gastric and intestinal juices, and its major constitutive elements are not absorbed from the gut into circulation significantly (M. Čolić, personal communication with Pavelic). Overnight incubation of clinoptilolite in acidic or weakly alkaline media at 37°C resulted in minimal amounts of soluble silicon (50-60 mg/L) (B. Subotić, personal communication with Pavelic). No traces of silicon have been detected in the serum of Wistar rats or CBA mice (I. Hršak personal communications with Pavelic) receiving clinoptilolite in food. However, zeolite particles were found in the first and second layers of duodenal cells. Cefali et al. [229], however, found elevated levels of silicon and aluminium in the plasma of experimental dogs ingesting synthetic zeolite A as a single dose. Likewise, Roland et al. [230] showed increased excretion of Si and Al in hens receiving zeolite A by intubation. Yet zeolite A is soluble, particularly in acidic media [231] in contrary to clinoptilolite that is basically not soluble at all.

The ion exchange behaviour of zeolites in the gut is complicated and a matter of growing interest. Many people want to see ion exchange in the gastrointestinal tract, but this capacity has been limited.

Table 1: Serum Clinical Chemistry Parameters in Mice Treated with Clinoptilolite

Parameters	24 h	7 days	3 months	6 months
AF (U/L)	92.4 ± 8.5	108.3 ± 11.4	41.2 ± 3.3	42.8 ± 0.60
Glucose (mM/L)	5.8 ± 0.8	5.3 ± 0.6	6.6 ± 0.9	6.0 ± 1.8
AST (U/L)	70.8 ± 4.3	76.2 ± 12.6	132.0 ± 41.9	70.8 ± 13.6
ALT (U/L)	28.6 ± 2.3	25.4 ± 3.1	59.0 ± 38.7	40.4 ± 4.3
Ca (mM/L)	2.14 ± 0.09	2.51 ± 0.12	2.38 ± 0.04	2.2 ± 0.2

AF, alkaline phosphatase; AST, aspartate aminotransferase; AL, alanine aminotransferase; Ca, total calcium. Source: M. Hadzzija, S. Krizzanac, toxicology study, Zagreb 1999, unpublished data.

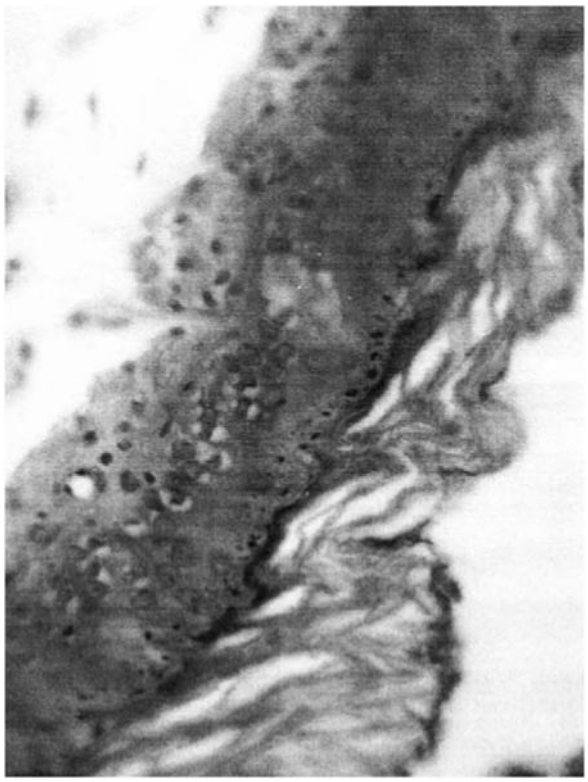

Fig.2: Photomicrograph of duodenum. (From unpublished data.)

Carbohydrates, starch, disaccharides, lactose and glycogen are a major source of energy in the body. Digestion of carbohydrate begins in the mouth by α -amylase from salivary glands. Acidity of the stomach inactivates α-amylase. Digestion of carbohydrate is continued in the small intestine by pancreatic α -amylase. The products of luminal hydrolysis are substrate (disaccharide) for enzymes from the brush border of enterocytes. α -glucosidase is one of four disaccharides. This complex of enzymes are involved in degradation of oligosaccharides from the digestive tract and in one step of degradation of glycogen in the liver. Pavelics results showed (data not publish) that clinoptilolite had no influence on the catabolic concentration of α -glucosidase on the brush border enterocytes, but neutral α -glucosidase was significantly reduced in the liver during the first 24 hours of treatment.

2.2. Toxicity tests

In the cyto-toxicity test there was no biological, toxicological damage to the test cells [5]. In activated clinoptilolite there are no small needle shaped particles (that are considered to be toxic or carcinogenic [Guthrie studied the correlation between particle shape and toxicity 122]) [90]. Pond and Yen in their study on reproduction found no toxicological or teratogenic effect from the clinoptilolite administered. During the toxicological studies by Pavelic et al [9] neither histopathological nor macroscopic changes to liver, pancreas, kidney and all other organs examined were determined after the administration of very high doses (3.3 up to 16 grams of micronised zeolite per day per Wistar rat) over a period of one year. Also in further experiments by Pavelic et al [8], [9], [10] on toxicology the lack of pre-clinical toxicity was clearly documented.

In human medicine, zeolites have been used as antidiarrheal remedies [3], for the external treatment of skin wounds and athletes foot, and in kidney dialyses for the removal of ammonia ions from body fluids. There were some data showing the systemic effects of zeolites on physiological systems of the body. The beneficial effects of zeolites on hematopoiesis, and various disease states, including tumors [8], have been observed. No toxic effects were observed in the toxicology study of clinoptilolite by Pavelic et al. [8, 9, 10]. The physical status of examined animals showed no evidence of any harmful reaction during the studies.

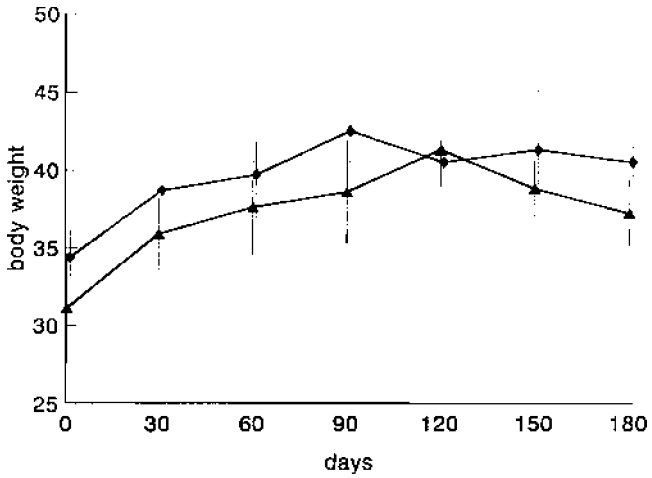

Fig.3 The body weight gain of control (diamond) and clinoptilolite treated (triangle) male CBA mice fed with 25% of clinoptilolite during 6 months. (From unpublished data.)

Clinoptilolite is well suited for these applications because of its large pore space, high resistance to extreme temperatures, and chemically neutral framework. There are a few toxicology studies of clinoptilolite obtained from different locations. The conclusion from all of them is that natural clinoptilolite is not toxic and can be used in human as well as in veterinary medicine. Here we will describe the preclinical toxicology of clinoptilolite from Vranje, Southern Serbia, by setting the "limit"-test. This refers to administering high doses of clinoptilolite (2x200 and 2x500 mg/mouse per day orally by gavage) for 6, 14 and 30 days. Since the clinoptilolite did not cause death of mice in this "limit" test, an "up and down" test on mice was performed, with daily doses ranging from 60 to 4000 mg/mouse. Again, no toxicity was observed. Classical acute, subacute and chronic toxicity studies on mice and rats of both sexes (separately) were performed. The duration of the study was as follows: acute, 1 month; subacute, up to 3 months; chronic toxicity up to 6 months. Animals were monitored for: phenotypic changes, changes in behaviour and survival, changes in body weight, amount of food and water consumed, changes in haematological and serum clinical chemistry parameters (erythrocytes, leukocytes, platelets, hematocrit, haemoglobin, glucose, alkaline phosphatase, aspartate

aminotransferase, alanine aminotransferase, bilirubin, inorganic phosphorus, and calcium), and urine clinical chemistry parameters (glucose, proteins, urobilinogen, bilirubin, nitrites, erythrocytes, leukocytes, pH, and specific gravity). Pathohistological analysis of liver, spleen, kidney, brain, lung, testes, ovary, duodenum, eye, stomach, large and small intestine, muscles, myocardium, pancreas, thymus and axillary lymph nodes was carried out on sacrificed experimental and control mice.

The results of all of these studies were that oral (in diet) administration of clinoptilolite to mice and rats for 6 and 12 months, respectively, caused no changes that could be considered a toxic effect of treatment.

Martin-Kleiner et al. [228] compared the effects of two preparations of clinoptilolite differing in particle size on serum chemistry and hematopoiesis in mice. One preparation was a powder obtained from tribomechanical treatment (MTCp) of the clinoptilolite and another was normally ground clinoptilolite (NGCp). Young adult mice were supplied with food containing 12.5, 25 or 50% clinoptilolite powder. Control animals received the same food, ad libitum, without the clinoptilolite. Clinoptilolite ingestion was well tolerated, as judged by comparable body masses of treated and control animals. A 20% increase of the potassium level was detected in mice receiving the zeolite-rich diet, without other changes in serum chemistry. Erythrocyte, haemoglobin and platelet levels in peripheral blood were not significantly affected. NGCp caused leukocytosis, with concomitant decline of the GM-CFU content in the bone marrow, which was attributed to intestinal irritation by rough zeolite particles. The MTCp preparation caused similar, albeit less pronounced changes. In a limited experiment, mice having transplanted mammary carcinoma in the terminal stage showed increased potassium and decreased sodium and chloride levels, severe anemia and leukocytosis, decreased bone marrow cellularity and diminished content of haematopoietic progenitor cells in the bone marrow. The clinoptilolite preparation ameliorated the sodium and chloride decline, whereas the effects of hematopoiesis were erratic [228].

In experiments on healthy CBA/H Zgr mice of both sexes over 6 months, various parameters were controlled which were anticipated to cause eventual clinoptilolite toxicity, which was added daily to the food or by gavage. The effect of the clinoptilolite was studied as a function of body weight gain. Body weight gain was slightly elevated for both treated and control animal groups, and differences were not statistically significant.

According to research protocol, every 14 days the mice spent 24 hours in metabolic cages. During this time, the quantities of food and water consumed and urine and feces excreted were measured. The results showed that, on average, nontreated (control) mice ate 3.3 g food, drank 3.8 mL of water, excreted 1.7 g of feces, and urinated 1.3 mL of urine. Over the course of 6 months, there were no differences between clinoptilolite-treated (per os) and untreated mice.

Clinoptilolite was given to the mice as a powder mixed with standard food at the ratio of 25% clinoptilolite. The treatment was continued during the prepregnancy and pregnancy periods, and during the lactation period.

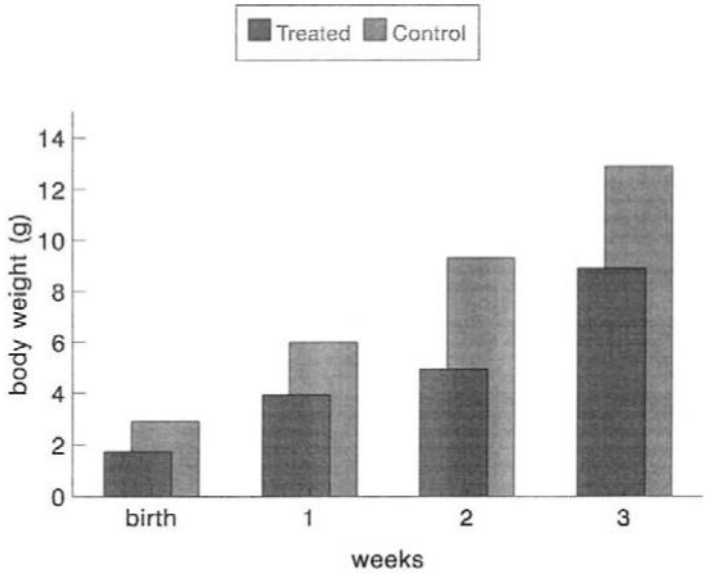

Fig.4 The average of born body weight and a gain in body weight of control and clinoptilolite-treated mice. (From M. Slijepc6evic, A reproductive/development toxicity study, Zagreb 1998, unpublished data).

Special consideration was given to the teratologic influence of zeolite on organogenesis (from 6 to 16 days of pregnancy). The prepregnancy period in mice treated with clinoptilolite was shorter than in control nontreated mice. The number of pups per litter (both before and after birth) was increased in clinoptilolite-treated mice. In addition, the average body weight of pups was lower (on average 100 mg/pup). In conclusion, the clinoptilolite equalized (regulated) and shortened the pre-pregnancy period. The number of pups per litter was increased in clinoptilolite-treated mice. Decreased birth weight may have been a consequence of increased number of pups per litter. However, there were no differences between control and treated animals that would suggest reproductive toxicity attributable to the clinoptilolite during the period of organogenesis. Regarding other parameters, including teratogenesis, clinoptilolite-treated mice were not different from control mice and did not show negative results, which suggests no attributable toxicity of clinoptilolite on reproduction

Table 2: Duration of Prepregnancy and Pregnancy Period (days)

	Prepregnancy and pregnancy period (cycles)			
Groups	1st	2nd	3rd	4th
Treated[a]	24.0 ± 3.8	24.3 ± 1.0	25.5 ± 1.9	26.4 ± 1.8
Control	56.8 ± 8.1	32.5 ± 11.2	43.2 ± 4.8	21.2 ± 0.4

*Mice fed with the food supplemented with 25% of the clinoptilolite. Source: M. Slijepccevic´, reproductive development toxicity study, Zagreb 1998, unpublished data.

Arscott found that broiler chickens fed a diet of 5% clinoptilolite from the Hector, California, deposit gained slightly less weight over a 2-month period than birds receiving a normal diet, but average feed-efficiency values were noticeably higher. Perhaps of greater significance is the fact that none of the 48 test birds on the zeolite diet died during the experiment, while three on the control diet and two on the control diet supplemented with antibiotics succumbed. In addition to an apparent feed-efficiency increase of 4 to 5%, the presence of zeolite in the diet appears to have had a favourable effect on the mortality of the birds [237].

Experiments evaluated the use of zeolites in the diets of young and mature Yorkshire pigs in 60-day and 79-day experiments, respectively, and found that the weight gain of animals of both ages receiving diets containing 5% clinoptilolite from Futatsui, Akita Prefecture, Japan, was from 25 to 29% greater than that of animals receiving normal diets [238]. Studies [239] found that the digestibility of crude protein and nitrogen-free extracts tended to be improved as zeolite was substituted for wheat bran in swine diets at levels from 1 to 6% over a 12-week period. Toxic or other adverse effects were not noted for any of the test animals described above. On the contrary, the presence of zeolites in swine rations appears to contribute measurably to the well-being of the animals. According to Torii [240], tests carried out at the Keai Farm near Moioka, Iwate Prefecture, Japan, where 4,000 head of swine are bred, showed that the death rate and incidence of disease among animals fed a diet containing 6% clinoptilolite was markedly lower than for control animals in experiments conducted over a 12-month period. The decrease in the number of cases of gastric ulcers, pneumonia, heart dilation, and in the overall mortality rate is remarkable.

Although no control groups were monitored, Morita [241] reported that the addition of zeolite to the diet of piglets severely afflicted with scours markedly reversed the progress of this disease within a few days. Four underdeveloped Laundry pigs were fed a diet containing 30% zeolite for the first 15 days and 10% zeolite for the remaining part of a month-long experiment. The severity of the disease decreased almost at once, and feces of all pigs were hard and normal after only 7 days. Although the pigs consumed an average of 1.75 kg of zeolite/head/day, no ill effects were noted, and once they had recovered from diarrhetic ailments, the pigs regained healthy appetites and became vital.

Experiments at the Ichikawa Livestock Experiment Station, where 400g of clinoptilolite was fed each day to pregnant sows and continued through the 35-day weaning period of their offspring, showed substantial increase in the growth rate of the young pigs. The authors reported that young pigs whose dams received the zeolite diet also suffered almost no attacks of diarrhoea, while those in control groups were severely afflicted with scours, greatly inhibiting their normal growth. Similar studies were conducted at Oregon State University (England, 1975) with young swine using rations containing 5% clinoptilolite from the Hector deposit. Although lesser in- creases in growth rates were found than in the Japanese studies, the incidence of scours was significantly reduced for animals receiving the zeolite diet. [234]

In 1969 Kondo et al. [242] found that clinoptilolite added to the feed of young calves improved their growth rate by stimulating appetite and decreased the incidence of diarrhoea and soft-feces. No deleterous effects were noted, and the feces of the test animals contained slightly less water and fewer particles of undigested solids in the >5 mm size-range. The incidence of diarrhea and soft-feces was markedly less in zeolite-fed calves than in control animals.

Earlier studies in the 1970s in the United States showed that as much as 40% clay could be added to animal rations without adverse effects [244].

2.3. Tolerance, side effects, interactions

Zeolite is considered to be a harmless substance [111]. One of the first uses on humans on a large scale was in Russia in 1986 after the Chernobyl disaster when for the Cs decontamination of children 2-30 volume percent of pure and powder clinoptilolite was added to chocolate and biscuits [84]. Many authors determined a good tolerance and almost zero side effects after studies on humans and animals. [46, 48, 52, 53, 54, 55, 56].

Rodriguez-Fuentes et al studied the effectiveness of clinoptilolite on acute cases of diarrhoea [3]. A clinical study was performed on 434 patients with acute diarrhoea caused by food poisoning. Along with a description of the use for fast recuperation most patients showed a good tolerance. No

participant dropped out of the study due to side effects. It was also proven that there was no interaction with the antibiotics tetracycline and chloramphenicol. In vitro a minimal adsorption was shown of Aspirin, Theophyllin, Propanolol and Phenobarbital. Currently there is another publication on an antacid (as therapy for patients with an excess of HCL in gastric juice) based on clinoptilolite [4], here no side effects were observed.

Hecht determined no serious side effects in a study on 62 patients that were administered natural clinoptilolite in either capsule or lozenge form over a period of up to one year. None of the persons interrupted or discontinued the intake.

The interaction of drugs in the gastrointestinal tract, where the main danger is the possible reduction of availability of some ingredients, can be easily predicted due to the cationic exchange capacity of clinoptilolite. In a few medicaments that contain metal ions as for example Lithium or Cis-platinum an interaction can be assumed. But due to the molecular size of most medicaments an interaction with clinoptilolite is very unlikely.

Farias et al studied the interaction between Metronidazol respectively Sulfamethoxazol and clinoptilolite and have positively evaluated the simultaneous administration.

Due to the effective location in the gastrointestinal tract of clinoptilolite the interaction with medicaments that are administered intravenously does not come into question, unless the medicament is based on a planned reabsorption in the enterohepatic circulation. The risk of interactions with medicaments administered per os can in any case be minimised by a delayed administration.

One of the major concerns that arise from the dietary use of zeolites is whether they have any adverse influence on the effectiveness of various medicaments when they are simultaneously administrated to the animals via feed and many experiments have been conducted lately in this area. Indeed, zeolites' non-specific adsorption property and cation exchange capacity could raise potential risks concerning the availability of medicaments used in on-farm strategic medication programmes for performance enhancement and health status preservation. Even if the cross-sectional diameter of a drug molecule is incompatible with the entry channels of the zeolitic structure—in this case being unable to pass through and being adsorbed on inner surfaces of the zeolitic matrix—the aforementioned consideration cannot be precluded since the external surface of the zeolitic particles is also offered for potential drug–zeolite interactions [189] and [190].

Rodriguez-Fuentes et al. [3] tested the potential interference of a natural zeolite with the bacteriostatic effect of tetracycline and chloramphenicol used in minimum inhibitory doses. The simultaneous presence of clinoptilolite–heulandite enriched zeolite and antimicrobials in Vibrio cholerae serotype 01 cultivations did not ameliorate the total inhibition of bacteria growth. Adversely, in vitro studies conducted by the same authors indicated that the zeolitic material slightly adsorbs Theophyllin, Propanolol and Phenobarbital. Interestingly, Lam et al. [190] demonstrated, through quantum mechanical calculations, the possibility of the adsorption of Metronidazol on clinoptilolite and suggested that the principal interaction stands at the formation of hydrogen bonds and coulombic forces among groups of the Metronidazol molecule and the external surface of the zeolitic matrix. However, in experiments which were carried out in aqueous medium simulating pH and temperature conditions of human gastrointestinal tract, the adsorptive behaviour was basically related to the zeolite's level of purification, as in the case of Metronidazol, and moreover to the polarity of the molecules, since no interference with Sulfamethazole was confirmed [191]. Both antimicrobials have molecule dimensions which are too large to enter the channels of the natural clinoptilolite used in these experiments, implying that potential interactions concern the outer surface of the zeolite, including the mesoporosity. However, the amphoteric character shown by natural zeolites as a consequence of their bufferant behaviour in an aqueous solution, suggests that they could attenuate the side effects derived from gastrointestinal sharp pH changes, favouring the absorption of some simultaneously administered drugs.

Furthermore, the potential interaction of clinoptilolite and antimicrobials was also tested in field studies. From a clinical point of view, the study of Papaioannou et al. [135] established the absence of any interactive effect of clinoptilolite on the availability of chlortetracycline in sows which were on a diet supplemented with both additives, since the beneficial effect of chlortetracycline (800 mg/kg feed) on the sow's health status during lactation was not inhibited by the concurrent use of clinoptilolite (2% inclusion rate). Similar results, concerning health status and performance evaluation, were also obtained in weaned, growing and finishing pigs fed diets supplemented with a clinoptilolite-rich tuff (at a rate of 2%) along with enrofloxacin (50 mg/kg of starter feed) or salinomycin (60 and 30 mg/kg of growers' and fatteners' feed, respectively) [135]. An additive net effect or an "enhanced-by-clinoptilolite" enrofloxacin efficacy was also proved in the case of post-weaning diarrhoea syndrome, supporting the results of a previous research [192], in which the concurrent use of a clay and lincomycine in the starter diet resulted in an additive net effect on the improvement of feed efficiency.

2.4. No interaction with vitamins and the like

Clinoptilolite has a high affinity to heavy metals and radioactive cations. Vitamins, amino acids and polyunsaturated fatty acids are in contrast not eliminated from the body. This is confirmed by a study by Papaioannou et al [1]. In this controlled study of 24 pigs, the effects on vitamin A, vitamin E, potassium, sodium, phosphorous, calcium, magnesium, copper and zinc in blood were determined during a long-term addition of 2% clinoptilolite to the fodder No significant changes to the vitamin and mineral concentrations in blood and liver and kidney tissue were determined. The result was also confirmed in a further study on dairy cows [2].

Katsoulos et al measured the long-term effects on blood values (haematocrit, haemoglobin, number of leucocytes) by fodder addition with healthy cows. All results clearly showed that the addition of 1.25% and 2.5% of clinoptilolite to the fodder had no effect on the blood parameters [11].

Changes in Haematological Parameters

Duration the toxicity study animals were monitored for haematological parameters. The number of erythrocytes in mice treated and not treated with zeolite for 6 months was not different. Also, leukocyte counts in the mice were not significantly different. Lymphocyte and leukocyte mononuclear cells made up about 90% of the white cell population in mouse peripheral blood. The platelet count also was not different in control and in clinoptilolite-treated mice (see Table 3) Table 3 in spite of intensive megakariocytogenesis in the spleen. Haemoglobin concentrations in both groups of mice were slightly lower than published values, but the two groups were not statistically different

Table 3: Hematology Parameters in Blood Sample

Group of mice	ERC(10^{12}/L)	L ((109/L)	Hgb (g/L)	TRC (10^9/L)
Control	5.2 ± 0.3	4.7 ± 0.3	± 11.3	327 ± 29
30th day	5.6 ± 0.6	4.1 ± 0.9	± 4.5	375 ± 56
90th day	5.2 ± 0.6	3.8 ± 0.8	± 2.4	376 ± 46
180th day	5.3 ± 0.7	5.9 ± 0.1	± 13.1	316 ± 50

ERC, erythrocyte; L, leukocytes; Hgb, hemoglobin; TRC, thrombocytes.
Source: M. Hadzzija, S. Krizzanac, toxicology study, Zagreb, 1999, unpublished data.

In general, clinoptilolite particles have been found to cause less irritation and tissue damage than the rod- and fiber-shaped particles of other natural zeolites such as erionite or mordenite, which resemble the asbestos fibers in morphology.

Serum Clinical Chemistry Parameters

Mice were killed at various times during the 6 month toxicological study. The serum obtained was analyzed for a number of biochemical parameters that would indicate the degree of damage to vital organs and metabolic function. The parameters were: alkaline phosphatase (AF), glucose, aspartate aminotransferase (AST), alanine aminotransferase (AL), and total calcium (Ca). The results indicate that there were no changes in these parameters during the 6 months. The value of AST was somewhat raised during days 1 and 7 of the experiment, which could be explained by adjustment of the mice to the new type of diet (maybe less food was consumed during the first month). But, after 6 months there were no changes). Urine analysis did not show any changes in glucose, bilirubin, ketonic bodies, erythrocytes, urobilinogen, nitrites or leukocytes.

2.5. Local Application

Long-term experience with locally applied zeolite on humans also showed no local irritation or contact dermatitis of the skin or mucous membrane in the mouth area [105]. Local tolerance as well as repeated-dose dermal tolerance testing was performed on mice and rats to ascertain whether the zeolite is tolerated at the sites that may come into contact with the product as a result of its administration [227]. The clinoptilolite was neither toxic nor allergenic to skin [222].

3. EFFECTIVENESS, INDICATIONS

3.1. Absorber and Ion exchanger

Many toxic heavy metals have been introduced into the environment by industrial effluent, ground and water contamination [91,111] that can accumulate in organisms and cause numerous diseases and disorders [92,111]. The toxic properties of heavy metals in animals and humans are well documented (e.g. Lead: [101, 114, 115, 116]). There are many methods to remove dissolved heavy metals [in fluids], amongst them ion exchange, excretion, phyto-extraction, ultra-filtration, reversed osmosis and electro-dialysis [93, 94, 95, 96].

The basis of certification of clinoptilolite as a medical device is the unique physical effect mechanism in the human (and animal) gastrointestinal tract as a cation exchanger and adsorbent especially in regard to NH_4^+, Pb^{2+}, Cd^{2+}, Cs^+ [12]. This ion exchange property of zeolite has been known for a long time and has been studied by many authors [112,113]. Adsorbents are substances that can bind dissolved, dispersed or gaseous materials as e.g. activated charcoal, alumina, dispersed silicon, kaolin and natural zeolite clinoptilolite. Of all the zeolites clinoptilolite carries out the ion exchange at the highest speed [41].

Both the ion-exchange and adsorption properties of natural zeolites can be exploited to make more efficient use of feed nitrogen in animal nutrition, to reduce intestinal diseases prevalent in young swine and ruminants, to control moisture and ammonia content of animal manure, to purify recirculating hatchery waters in aquaculture, to provide oxygen-enriched air for fish breeding and transportation, and to reduce the nitrogen content of feedlot- and hatchery-runoff waters. [234]

The selectivity sequence of natural zeolite clinoptilolite is as follows:
(Si/Al = 4.2): $NH_4^+ > Pb^{2+} > Na^+ > Cd^{2+} > Cu^{2+} \approx Zn^{2+}$ [66].

The highest affinity is therefore ammonium, followed by lead, sodium and cadmium. In an advanced study on cation exchange capacity of zeolites Miles determined the following selectivity sequence for clinoptilolite:
Cs > Rb > NH^4 > Sr > Na > Ca > Fe > Al > Mg > Li. [70]

The release is in reverse order. If for example clinoptilolite already has Ca and Mg adhesion and it meets e.g. NH^4 then it releases the Ca and Mg and absorbs the NH^4 instead, due to the cation exchange principle.

3.2. Detoxification

The detoxification property of natural clinoptilolite zeolite is not only fulfilled by its adsorption and ion exchange function but also by the physical crystal surface effect of the clinoptilolite zeolite and SiO_2 ([41], S. 268ff). Jovanovich et. al. found out that the adsorption potential of the surface treated [note : micronised] zeolite (esp. clinoptilolite) was significantly higher than untreated zeolites. [69]. Nikolajev und Mayanskiy [51] also wrote on the effect of zeolite on the human body, that along with the already mentioned alkaline and earth alkaline cations of natural clinoptilolite it also has a structure of negatively charged polyanions that when ground become a bioactive surface which gives the zeolite a detoxicating effect in terms of cleaning the organism.

Shalmina und Novoselov described in 2002 [50] the detoxification mechanism of natural clinoptilolite zeolite in different forms of endotoxicosis in human and animal organisms.

Table 4: Endotoxicosis

Endotoxicosis from	**Mechanisms for eliminating the toxic substances with clinoptilolite zeolite**
Endotoxine, z.B. Endotoxins e.g. acidosis products, bacterial endotendotoxins, free radicals, metabolic products	Adsorption in the macro and meso pores of natural clinoptilolite zeolite
Exogenic toxins	Adsorption in the macro and meso pores of natural clinoptilolite zeolite
Low molecular compounds e.g. Nh_3, H_20, Cd_4, Ch_4	Adsorption in the macro and meso pores of natural clinoptilolite zeolite
Biogenic macro and micro elements in excessive concentration	Ion exchange

3.3. Aflatoxins and mycotoxins

In the recent years many investigators are trying to solve the worldwide problem of high incidence rates of contamination of cereal grains and animal feed with mycotoxins and the zeolites seem to be the great solution. For example, molecular sizes of aflatoxins range from 5.18 Å (B1 and B2) to 6.50 Å (G1 and G2) and only zeolites with entry channels wide enough to permit the diffusion of aflatoxin molecules to the intracrystalline structure are capable of demonstrating a clear sequestering effect [135]. Clinoptilolite, a natural zeolite, has high adsorption indexes in vitro, more than 80% for aflatoxins B1 and G2 and the adsorption process begins with a fast reaction whereby most of the toxin is adsorbed within the first few minutes (35). The in vivo efficacy of zeolites to ameliorate the consequences of aflatoxicosis, mainly in poultry, has also been verified in many cases.

3.4. Ammonium bonding

The mechanism of bonding ammonium has been known in medical technology for a long time. Already in 1975 a method to remove ammonium ions from the dialysis fluid of a circulatory haemodialysis system was patented (DE 2512212) by Andersson und Grenthe [23]. Patzer et al proved in 1995 a quick adsorption of ammonium by clinoptilolite. The column of clinoptilolite pellets retained the ammonium exchange capacity for 6 exchange- respectively regeneration- cycles. Natural zeolite clinoptilolite protects against ammonium toxicity in rats [117] and sheep [118]. Narmandakh et al proved that the ammonium concentration in the rumen of sheep could be reduced by the addition of natural zeolite to 6-10 mol/L compared to 17,5 mmol/L in the control group within 1.5 to 3h. [78] Armbruster confirmed that clinoptilolite reduced the ammonium toxicity in the gastrointestinal tract of pigs and sheep whereby the possibility of use is not limited to animals [12].

Panaceo zeolite clinoptilolite has the ability to adsorb a part of the ammonium ions resulting from protein decomposition in the gastrointestinal tract and in this way alleviate the liver through lesser ammonium resorption. This effect is important for all types of liver disease and also by Cor pulmonary important and significantly contributes to an improvement of the general condition and mental elucidation (ammonium is common in fluids, an increase in blood leads to amentia, sleepiness all the way to coma depending on amount).

White and Ohlrogge [233] first stated that ammonium ions formed by the enzyme decomposition of non-protein nitrogen were immediately ion exchanged into the zeolite structure and held there for several hours until released by the regenerative action of Na+, entering the rumen in saliva during the after-feeding fermentation period. From both in vitro and in vivo experiments they found that up to 15% of the NH4 in the rumen could be taken up by the zeolite. These observations were the causation for the conduction of many experiments in order to determine the influence of zeolites on rumen NH4 concentration and their potential use for the counteraction of the toxic effects of urea inclusion in ruminants' rations.

In this same area Watanabe et al. [243] raised six young bullocks for 329 days on a diet containing 2% clinoptilolite, diarrhea and other intestinal ailments were noticeably less prevalent in the animals on the zeolite diet, and the excrement from these animals was significantly less odoriferous, again testifying to the retentivity of clinoptilolite for ammonia.

Hemken et al. [136] showed that supplementation of 6% clinoptilolite, in the ration of dairy cows containing urea, significantly reduced rumen NH3 concentration. The same trend was observed by the dietary addition of 5% clinoptilolite in steers [147 (review of 243)] and lambs [148]. Furthermore, clinoptilolite was effective in reducing rumen ammonia concentration even when no urea was present in the ration of steers receiving a high concentrate diet, and that this reduction was linearly associated to the percentage of clinoptilolite inclusion [149]. Nestorov [150] referred that simultaneous administration of clinoptilolite and urea in sheep protects rumen flora from toxic effects of ammonia by inhibiting the reduction of microbiota population.

The binding of ammonium to zeolites has been noted in pigs as well, and many researchers suggested this action as the possible mechanism for the observed improved performance of the animals receiving zeolites. There are evidences that clinoptilolite elevates nitrogen excretion in feces [139, 154] and reduces the ammonia concentration in blood serum [139, 137, 155], when supplemented to the basal diets of pigs. Furthermore, Pond et al. [156] and Yannakopoulos et al. [157] found that clinoptilolite reduced the weight of the organs involved in the metabolism of ammonia (liver and kidneys), as the consequence of the reduced ammonia concentration in the gastrointestinal tract. Such observations result from the direct binding of NH4+ to zeolites, as clinoptilolite has no adverse effect on the ureolytic bacteria of the large intestine and urease activity [158].

3.5. Organophosphate poisoning

The dietary use of clinoptilolite appears to be effective in the prevention of organophosphates poisoning. Experiments in sheep have shown that the oral administration of clinoptilolite at the dose of 2 g/kg of body weight, earlier or simultaneously with an organophosphate (VX), partially protects from poisoning by inhibiting the decrease in cholinesterase activity [159] and by protecting rumen flora [160]. The protective effect of clinoptilolite on cholinesterase activity has been observed in mice receiving higher doses of organophosphates as well [161, 162].

3.6. Heavy metal bonding

The high affinity of clinoptilolite to heavy metals [67, 71, 72, 73, 74, 75, 76, 77 and more] causes them to be attracted to the crystal grid and bonded there and finally to be excreted with the zeolite. This cation exchange mechanism takes place according to a selection sequence [see point "adsorber and Ion exchanger2] that prefers an absorption of heavy metal cations and radioactive substances from the chyme and at the same time protects or better ignores trace elements and vitamins. The silicon compounds in the crystal grid have a very high adsorption capability that is less for the alkaline cations in the crystal grid e.g. K^{+}, Na^{+}, Ca^{++}, Mg^{++} etc. as for heavy metals and ammonium ions e.g. Cd^{++}. Hg^{++}. Fe^{++}. Pb^{++}, Cu^{++}, $Nh4^{+}$ und also against radioisotopes (e.g.. Cs^{+}, Sr^{++} [68]). The ion exchange can take place in the **b**ody fluids such as lymph, blood and digestive juices for example in the stomach or through the intestinal villi. It can therefore work selectively in the organism, a property that is exclusive to natural clinoptilolite and can not be achieved by artificial zeolite or any other absorber. [41]

In a simulation of the human digestive system it was shown at pH 1.5 (simulation of the stomach milieu) that clinoptilolite had an exceptionally good adsorption capability for lead (32%) and mercury (57%). At a PH value of 8.1 (small intestine) lead (86%) and mercury (45%) are also absorbed well while the concentration of zinc and cadmium showed no further reaction. The absorption of ammonium however in this milieu increases to 36% [20].

In the breeding of pigs the lead values in liver and kidneys could be reduced with an addition of 1% clinoptilolite to the fodder with a content of 500 or 1,000 ppm lead [17, 119].

The clinical relevance of the lead adsorption in the gastrointestinal tract is underlined by several publications that describe the exposure of the average population to lead through the respitory system and through nutrition as approximately balanced [31]. In acute cases of lead poisoning headaches and neuropathy are come especially to the forefront. In the long-term anaemia can occur with less concentration in the blood, in children it often leads to behavioural disorders and difficulties in learning. As shown by Fertmann et al [27] the amount of lead in the blood correlates to the amount of lead in drinking water. In old buildings lead pipes are still common.

Zeolites, due to their high ion-exchange capacity, have been used effectively for the prevention of heavy metal toxicity in animals. Pond et al. [163] found that clinoptilolite protects growing mice from lead (Pb) toxicity when added to their ration in such quantities that the ratio clinoptilolite/Pb to be 10/1. According to Pond et al. [164], similar protection is provided in swine as well. The selectivity of clinoptilolite for cadmium (Cd) and Lead (Pb) has been studied in vitro in order to be investigated whether its use reduces the levels of these elements in rumen and abomasal fluid. The experiments showed that clinoptilolite bent the 91% of Pb and the 99% of Cd in rumen fluid within 24 h, and in the abomasal fluid the 94% of Pb within less than 1 h [165].

The results of these experiments suggest the feasibility of using zeolites and mainly clinoptilolite as a feed additive in the prevention of certain types of heavy metal intoxications in farm animals or in aquatic biological systems, as is the case in the study of Jain [166], where is ascertained the capacity

of zeolite to enhance the removal of Pb from water, thus decreasing its availability to the teleost fish Heteropneustes fossilis.

3.7. Bonding and elimination of radioactivity

Apart from heavy metals, zeolites can also bind radioactive elements, thus being suggested as a means of altering their uptake and excretion from the body. As could be seen in the selective sequence of the raw material the zeolite used also had a high affinity to radioactive cations (caesium). Approximately 500,00 t (especially clinoptilolite) were used in 1986 for the nuclear power plant catastrophe in Chernobyl, the largest part of it to build protective barriers and for agricultural purposes in the affected area [12]. Clinoptilolite was also used for the decontamination of drinking water. Apart from that the ^{137}Cs content of the drainage water of the casing of the reactor core could be reduced by 95% with clinoptilolite filters. In Bulgaria the caesium content of cow milk was reduced by a striking 30% by the addition of 10% clinoptilolite to the cow fodder. To decontaminate children chocolate and biscuits were prepared with 2 to 30 percent by weight clinoptilolite.

The efficacy of clinoptilolite against Cd toxicity has been proved in pigs, The authors observed that 3% clinoptilolite supplementation prevented the cadmium-induced iron deficient anemia in growing swine that were receiving 150 ppm $CdCl_2$ [168].

Zeolitic matrix exchanges radio-nuclides in the gastrointestinal tract and is excreted by normal processes, thereby eliminating radioactive elements' assimilation into the body. Arnek and Forsberg [169] proved the selectivity of some natural zeolites such as clinoptilolite, chabazite and modernite for cesium. Gomonaj et al. [170] proved the selectivity of clinoptilolite for strodium and zirconium. Phillippo et al. [171] showed that the dietary use of clinoptilolite may constitute a simple and cost-effective method for minimizing the adsorption of radioactive cesium by sheep grazing contaminated pastures, although there might be no effect on cesium already been built-up in the body due to a previous exposure. Furthermore, Forsberg et al. [172] observed that the administration of mordenite in sheep and goats increased the excretion of cesium with feces and reduced its accumulation in tissues.

3.8. Impact on parasite infections

Considering the potential efficacy of zeolites against parasite infections, the results of the experiments first conducted in rats were encouraging for their use in other animal species as well. According to Wells and McHugh [178], the administration of clinoptilolite at the rate of 10% of a conventional diet facilitated the removal of parasites from the intestinal lumen of rats infected with the nematode Nippostrongylus brasiliensis. Furthermore, Wells and Kilduff [179] observed a more accelerated intestinal -d-glucosidase and aminopeptidase activity restitution in rats fed a commercial diet supplemented with clinoptilolite (5%) and recovering from N. brasiliensis infection. Confirming the observations in rats, Deligiannis et al. [180] recently proved the efficacy of clinoptilolite against parasite infections in growing lambs. They showed that feeding lambs, primarily infected with a single dose of gastrointestinal (GI) nematodes, with a concentrate mixture containing 3% clinoptilolite significantly decreased their total worm burden and faecal egg counts per capita fecundity and demonstrated that clinoptilolite supplementation reduced the establishment of GI nematodes and resulted in a good performance of the animals.

4. FREE RADICALS,

4.1. Formation and reactivity

Oxidative metabolism is on the one hand the most efficient way to provide energy in cells on the other the participation of oxygen brings the formation of free oxygen radicals (reactive oxygen species, ROS) with it that cause damage to biological structures, especially lipids, carbohydrates, proteins and deoxyribonucleic acids. [See also chapter “sport”].

The high reactivity is produced by the instable electron configuration of the radicals. They extract fast electrons from other molecules with which they collide. These molecules then become free reaction capable radicals themselves [58].

Free radicals are formed amongst others during the mitochondrial respiratory chain of the arachidon oxygen exchange by the activation of neutrophiles, by exposure reperfusion and metabolites of bacterial metabolism. Also nutritional components can favour radical forming reactions and triggering for example multiple unsaturated fatty acids and fats containing lipoperoxides. Also xenobiotics and pharmaceuticals can be converted to free radicals or stimulate the formation of radicals [89].

An increased release of ROS is contingent to environmental noxa (air pollution, heavy metals, pesticides), UV rays, fatty food, stimulants (tobacco, alcohol), inadequate physical training or also the metabolism of different medicaments (e.g. oral contraceptives). However also diseases on their part and damage to tissue lead normally to an increased formation of ROS [20].

4.2. Clinical pictures in conjunction with oxidative stress

When the normal oxidation-anti-oxidation balance is disturbed an uncontrolled attack of oxygen radicals on all cell components can occur [87, 88]. Lipids can be damaged by peroxidation of unsaturated fatty acids, proteins by oxidation of sulfhydral groups, carbohydrates by polysaccharide depolymerisation and nucleic acids by alkaline hydroxylation, , "nicking", "cross-linkage" und DNA breaks [87]. The danger potential for lipid peroxidation processes (especially with newborns) can today be considered as proven [97]. Free radicals can be held responsible for ischemia diseases of the gastrointestinal tract and cardial ischemia [97].

According to Zarkovic [102] *“reactions of free radicals in tissues are accompanied by oxidative reduction of polyunstaturated fatty acids in membrane lipids. This process leads to the production of highly reactive aldehydes that can be described as second messengers for the primary free radicals. The highly active aldehyde 4 hydroxynonenal (HNE) seems to be on of the main zytotoxic products that can be found in normal physiological conditions in tissue”*.

Oxidative stress plays a part in the creation of a series of (esp. degenerative) diseases: e.g. Arteriosclerosis (and consequently to heart attacks and strokes), diabetes mellitus, cataract (especially the retina is susceptible to radical damage [97], rheumatic diseases, premature ageing, neurodegenerative diseases, infectious and inflammatory diseases (endophtalmitis and uveitis [98,99] all the way to malignant tumours. Halliwell und Cross [28] are of the opinion that oxidative stress is by most diseases a secondary phenomena but empahise that it is of no less importance because of that. Each organ or tissue can become the target of an oxidative stress which can lead to the occurrence of different diseases. Skin (dermatitis, psoriasis), brain (Parkinson, alzheimer) liver (hepatitis C, haemochromatosis, pancreatits), kidney (glomerulonephritis), joints (rheumatic joint inflammation), gastrointestinal apparatus (diabetes), lung (asthma), blood vessels (arteriosclerosis), (eyes, cataract).

4.3. Anti-oxidants

There are several large studies in connection with the effects of anti-oxidants in this case with vitamin E, that according to the meta analysis and summary by Jialal and Devaraj [35] brings on average advantages with a α-Tocopherol supplementation for patients with coronary heart disease. Two studies (CHAOS and SPACE) showed a clear reduction of the cardiovascular deaths and the non lethal myocardial infarcts that were established as end points. The GISSI, ATBC and PPP studies showed no significant reduction in the primary end point but signifant advantages in regard to further clinical end points (GISS-Prevenzione Investigators 1999, The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group 1994, Collaborative group of the Primary Prevention Project PPP 2001).

CHAOS: Cambridge Heart Antioxidant Study (n=2002), [32].
SPACE: Secondary Prevention with Antioxidants of Cardiovascular Disease in Endstage Renal Disease (n=196), [34].
GISSI: Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardio (n=11324), [33].
ATBC: α-Tocopherol, ß-Carotene Cancer Prevention (n=29133), [38].
PPP: Primary Prevention Project (n=4495), [37].
HOPE: Heart Outcomes Prevention Evaluation (n=9541), [36].

In a further dose area (for adults: for vitamin E ≤1600 IU/d, for vitamin C ≤2000 mg/d) the safety of the supplementation of anti-oxidants is given [6].
The supplementation with vitamin C and E (≤400 IE) led in none of the studies to clinical disadvantages or to any dangerous or jeopardising effects (Jialal und Devaraj 2003).

The results of the vitamin C and vitamin E studies produced predominantly arguments for cardiovascular and general clinical advantages through the supplementation of anti-oxidants. As Jialal et al. in "Is there a vitamin E paradox?" [40] state: "In addition to epidemiologic studies that suggest a benefit for high intakes of alpha-tocopherol, studies of supplementation in humans have clearly shown that alpha-tocopherol decreases lipid peroxidation, platelet aggregation, and functions as a potent anti-inflammatory agent. In the five large prospective clinical trials with alpha-tocopherol therapy, four have shown a beneficial effect on cardiovascular end-points (two studies on a primary end-point and two studies on other cardiovascular end-points). Thus, the totality of evidence based on the epidemiologic data, in-vitro studies and animal models, and the clinical trials appears to support a benefit for alpha-tocopherol supplementation in patients with pre-existing cardiovascular disease."

There is general agreement on the fact that the potential of anti-oxidants lies more in the blocking of antherogenesis as in the prevention of acute vascular incidents such as heart attack or stroke. Thus the benefits of anti-oxidants can be seen in the prevention of the formation of new atherosclerotic plaques.

As Yossi Gilgun-Sherki et al .summarised [29] in Neuropharmacology in regard to neurodegenerative diseases: *"Due to increased exposure to environmental damage, our endogenous antioxidant defense system is not completely effective. It seems reasonable to propose that antioxidants are very important in diminishing the cumulative effects of oxidative damage. Since oxidative stress has been implicated in the pathogenesis of many neurological, particularly neurodegenerative, diseases, antioxidants of widely varying chemical structures have been investigated for use as therapeutic agents. Most of the papers hereby reviewed checked the efficacy of antioxidants in the treatment of neurodegenerative diseases. Although some showed a degree of efficiency when used in animal models or in small clinical studies, none of the antioxidants were examined in a large-scale controlled study and the data is conflicting."*

It can be assumed that it is absolutely reasonable to reduce highly excessive ROS levels (whether they are a result or cause of a disease) with anti-oxidants with acceptable or no side effects and thus aid the therapy of ROS associated diseases. Exactly this is the main medicinal purpose and asserted effect of this medical device: "Reduction of oxidative stress".

4.4. Possibilities to measure free radicals

The cell membrane consists mainly of unsaturated fatty acids that can react very quickly with radicals. Oxidation products are created from these membrane fatty acids the concentration of which can provide information on the degree of damage. By measuring the lipid peroxidation it can be determined how much the cell membrane has already been damaged by free radicals. A reduction in lipid peroxidation therefore means a reduction in damage to the cells and with that a massive alleviation.

Due to Timo Vuorimaa there are the following methods of measuring (…) oxidative stress and antioxidant defence [245]:*"The oxidative damage sustained by lipoproteins has been measured by a number of methods (Slater 1985). Serum diene conjugation has been found to be a useful method to estimate the level of lipid peroxidation (Vasankari et at 1995). It measures the early events of lipid peroxidation and might, therefore, be less sensitive to the numerous compensatory antioxidative mechanisms that occur in the organism and are a problem in some other measurements (e.g. thiobarbituric acid reactive material and fluorecent chromolipids); these methods measure end products of lipid peroxidation rather than the early phases of the process. However, all these commonly used analytical methods have some limitations and the main analytical question is unresolved. In addition to the influences of methodology, exercise intensity, training, nutritional status, and delayed-onset of lipid peroxidation after exercise might be responsible for inconsistency of results (Davies et at 1982, Haramäki and Packer 1994, Ji 1995)."*

As free radicals are themselves very instable and a quantitative measurement cannot be made or only with great difficulties, the extent of the damage by free radicals takes place with the measurement of the lipid peroxidation. In this regard, during the "clinical assessment" by Prim. Dr. Thoma a quantitative measurement was performed on 33 persons of hydroperoxide in capillary blood with the free radical analytical system (FRAS) to determine the oxidative impact. With the intake of zeolite by persons with serious illnesses the oxidative stress could be reduced by 63 U. Carr (21,3 %), by healthy persons by 83 U.Carr. (14,5 %) [20].

The method used to determine the free radicals (d-ROMs-Test) is described by Cesarone et al. [25] in *'A simple test to monitor oxidative stress'*. In this study the test persons were given a combination of 10 anti-oxidants for one week. Even with the supplementation of this "anti-oxidant cocktail" no significant larger reduction of the oxidative stress was achieved in comparison to the administration of clinoptilolite. This is further evidence of the effectiveness of clinoptilolite in vivo and an indication of the optimised effect in the combination of zeolite active in the gastrointestinal tract and other anti-oxidants active in blood.

4.5. Anti-oxidant clinoptilolite – prevention and reduction of systematic damages

Zeolite's site of action is the gastrointestinal tract. Here due to its microscopic structure with its enormous internal surface area (up to 1,000 m^2/g Zeolith) and cation bonding capacity it is in a position to physically reduce the creation of free radicals and to significantly reduce the resulting damages to biological structures by free radicals (e.g. lipid peroxidation of cell membranes, oxidation of the DNA alkalines). The effects of the damages caused by free radicals are not at all limited to the

gastrointestinal tract due to the intestinally resorbed peroxidised fatty acids and due to the typical chain reaction triggered by the free radicals. Zeolite is therefore also definitely in a position as a physical radical catcher working in the forefront of the gastrointestinal tract to reduce systematic damages. [18]

As described in the "Study of the anti-oxidative activities of Panaceo" [15], lipid peroxidation by free radicals is probably the most important process that leads to oxidative stress. The increase of lipid hydroperoxides produced postprandially (after meals) are resorbed in the small intestine and pass into the blood circulation. Panaceo causes a reduction in the production of lipid peroxidation products in the gastrointestinal tract. In tests appendages with the use of zeolite a reduced production of free radicals was determined whose origins were not in a chemical reaction but based on a physical mechanism.

The benefits for the user is the reduction of free radicals as clearly shown in both appendages.

5. CLINICAL APPLICATION

The result of the study on the anti-oxidative activities of Panaceo was that activated zeolite can not only quench radical precursors but also that it is in the position, due its cation bonding capacity, to reduce the catalytic formation of radicals from hyperoxides or other reactive oxygen metabolites (ROM) by bonding these ions with transitional metal ions (Cu^{2+} und Fe^{2+}).

Especially for patients that are in clinically critical situations or that are not able to neutralise the oxidative stress with own body resources zeolite can improve the therapy success or at least provide subjective relief (in terms of an improvement to the general condition). These observations are supported by the "clinical observation on the use of tribomechanically activated zeolite (Panaceo)" by Prim. Dr. Wolfgang Thoma from the Privatklinik Villach [19]. Records were kept over a period of 6 years on the effect of the complimentary use of clinoptilolite for a wide range of diseases.

5.1. bone density, osteoporosis

New studies (on rats) document an improved calcium absorption and an increase in bone density when clinoptilolite is administered. Clinoptilolite seems to support the storage of Ca in bones and can therefore improve bone density and effectively support the treatment of osteoporosis [17]. As part of the patent registration AT 06450185.1: "Use of zeolite in the therapy and prophylaxis of osteoporosis" in a well documented case an improvement in bone density from 67% of desired value to 79% of desired value in humans was determined within two years. In the meantime a clear improvement in bone density with the use of Panaceo clinoptilolite per os has been determined. With this a unique opportunity has been opened in the treatment and prevention of osteoporosis and in anti-aging, as a stable bone framework is the basis for a long and healthy life.

The dietary inclusion of synthetic zeolite A (at the rates of 0.75% or 1.5%) in broilers which are on a diet with inadequate or marginal levels of calcium results in an increase of bone ash content along with a reduction of rachitic lesions [183]. Accordingly, the incorporation of zeolite A in the same diets at 1% exerts a clear beneficial effect in reducing the incidence of tibial dyschondroplasia [183], [184] and [185]. Although tibial dyschondroplasia is a metabolic cartilage disease which represents the endpoint of several mechanisms, the incidence is increased when high dietary levels of phosphorus are used [186] or when dietary calcium is lower than 0.85% [187]. Similarly, the beneficial effect of zeolite A is inconsistent and largely depends on the dietary level of calcium. According to Watkins

and Southern [188], the dietary use of 0.75% zeolite A in broilers is accompanied by alterations in mineral absorption and tissue distribution, resulting in increased tibia ash and density and improved fresh tibia shearing force scoring, but only when dietary calcium ranges from 0.6% to 0.8%. In the same direction, the reduction in the incidence and severity of dyschondroplastic lesions in the research of Edwards [185] in broilers was associated with a zeolite-induced decrease in calcium, total phosphorus and, in particular, phytate phosphorus retention.

5.2. Irritable Bowel Syndrome

Schulz reported on his experiences in regard to the irritable bowel syndrome [in personal communication]: *"In the early phase of the irritable bowel syndrome more or less disturbed digestion processes lead to the formation of fermentation and putrefaction toxins. They destroy the intestinal milieu and lead to dysbioses, which promote maldigestion. As a further result there affections of the intestinal mucous membrane, changes in the resorption relationships, possible formation of the Leacky Gutt syndrome and finally the complete picture of the irritable bowel syndrome.*

The range of causes for the irritable bowel syndrome is very wide. It goes from chronic excessive demands on the intestinal tract by false nutritional habits (too fast, too much, too often, too late, too heavy), to psycho-emotional influences which are somatised in the intestinal tract, all the way to individual foodstuffs intolerance or allergies often brought about by environmental poisons (heavy metals, enzyme blockers etc.) which can lead to this complex clinical picture. Foodstuffs intolerances like lactose respectively fructose intolerance are clinically well researched and easily diagnosed. Very often intolerances can be found which often only occur temporarily and clinically can only be diagnosed by the IgG test or bioenergetic test methods and can practically apply to all foodstuffs.

A holistic approach as therapy concept for irritable bowels has proven to be of value in practice, with alleviation of the intestinal tract (individually adapted fasting cure), gentle cleansing of the intestinal channel, milieu sanitation, adjustment to an individually well tolerated, non mucous irritating, health promoting diet and a change in false behaviour patterns.

For approx. 3 years I have often and successfully been prescribing for irritable bowel syndrome PANACEO med powder (on empty stomach 3 x daily 1 heaped coffee spoon in the mouth and then drink water). In pronounced cases I prescribe additionally PANACEO med as capsules (3x3). In comparison to similar cases that I previously treated without Panaceo med I found a subjectively and objectively quicker healing of the irritable bowel symptoms."

5.3. Dietary use of zeolites on diarrhoea syndromes

One of the first wide uses in humans was the diarrhoea medicine Enterex [3]. Studies were preformed to test the use of clinoptilolite as a carrier for substances for a slow release to the body [85,86].

The physicochemical properties of ingested zeolites may result in intestinal lumen or even systemic effects affecting the biochemical processes, many of which are related to ion exchange, adsorption and catalysis. From this point of view, recent research efforts provide insights into theoretical mechanisms interpreting the supportive effect of the dietary use of zeolites on animal diarrhoea syndromes, such as sequestration and lack of cytotoxicity of enterotoxins, binding of endogenous substances implicated in gastrointestinal disturbances, earlier restoration of impaired digestive enzyme activity in animals suffered from diarrhoeas or reduction of nematodes' establishment in the gastrointestinal tract. Furthermore, zeolite-enriched diets exert a clear beneficial effect on the prevention of certain metabolic diseases in dairy cows, as recently evidenced by researchers who underlined the restrictive

role of zeolites in the bioavailability of dietary Ca as the interpreting mechanism in the case of milk fever and the improved dietary energy uptake as the one in the case of ketosis.

5.4. Effects on Diabetes Mellitus

Zeolites are of potential use in the treatment of diabetes. Our unpublished data concerning alloxan-induced diabetic mice showed that natural clinoptilolite could prevent or diminish some late complications of diabetes, namely development of polyneuropathies. Although the natural, finely ground clinoptilolite did not significantly decrease the blood glucose levels in our animals, there were some indications that zeolite did in fact sorb a small amount of the glucose. The hydrothermal transformation of natural, purified clinoptilolite using FeSO4 has been shown to cause selectivity for glucose adsorption [216].

Alloxan-induced diabetic mice spent 24 hours in metabolic cages during 6 days of clinoptilolite application. The measured volume of drinking water and excreted urine was decreased, and on day 6 these parameters were reduced by 50%.

Clinoptilolite showed positive effects on many diabetic symptoms. Significant differences between zeolite-treated and nontreated diabetic mice were noticed only in the amount of total Ca in sera. Nontreated diabetic animals had 1.92 mM/L Ca in sera, whereas clinoptilolite-treated diabetic mice had a higher concentration of Ca in sera, ranging from 2.15 to 2.3 mM/L. Iron (Fe2+) –containing, natural clinoptilolite interacts with glucose with formation of an iron-glucose complex in the clinoptilolite. The mechanism of action of the Fe2+- clinoptilolite-glucose interaction is a strong adsorption governed by the reactive characteristics of glucose [216, 217].

It is well known that administration of silica prevents almost completely the onset of spontaneous diabetes in young BB-rats [218]. Administration of silica particles prevents cell destruction in non-obese mice given cyclophosphamide [219]. Since silica is highly specific in its action against macrophages, this observation indicates an important role of these cells in the pathogenesis of the disease.

5.5. Possible Effects in Tumor-treatment

Development of modern industry causes increasingly serious pollution in the environment where human live in, constituting a catastrophic health risk including cancer. Anti-cancer is thus one of the challenges faced scientists in 21st century in the realm of life science, and removal of carcinogen from environment is an important step. Nitrosamines are probably the most widespread carcinogens, existing in workplace, processed meats, cigarette smoke and beer, and even are produced in the stomach by reaction of secondary amines and nitrite NO_2^-,both taken from foods [193.]. A report of German scientists showed in 1976 that the uptake of nitrosamines for a person was to 700 ng everyday. In another study, the mean total nitrosamines levels were 0.7 or 1.3–1.4 μM for fasting gastric juice at pH 1.0–1.5 or pH 3.6–7.0, correlated with bacterial mutagenicity of juice [194]. The occurrence of gastric cancer was mostly related to the nitrosamines in stomach, as reviewed in 1983 [195] and 1989 [196]. Many carcinogenic agents like nitrosamines or their precursors enter human stomach through diet and drinking, no matter how carefully human treat their food. Environmental pollution makes this hidden trouble more serious, because of the contaminated food and atmosphere. However, although nitrosamines are well-known carcinogenic substances, they require metabolic activation before reaction with DNA to cause mutation and cancer. Therefore, it is possible and

necessary to trap the nitrosamines in gastric juice provided a selective adsorbent material is employed. To seek this functional material, zeolites are considered as the best candidates.

Zeolites and molecular sieves have been employed in slow release drugs, enzyme mimetic drugs [197], anti-tumor drugs [198], and additive in cigarette to remove carcinogenic agents like nitrosamines [199, 200, 201, 202]. Apart from the trapping in gaseous phase, zeolites can also adsorb volatile nitrosamines like NDMA (N-nitrosodimethylamine) and NPYR (N-nitrosopyrrolidine) in organic or aqueous solutions [203], which is beneficial to eliminate the nitrosamines in beer [204]. Among these zeolites used NaY possesses the largest adsorption capacity in organic solution while ZSM-5 is the best adsorbent in aqueous solution.

Zarkovic et al (2003) [16] proved in vivo the anti-oxidative property of orally administered clinoptilolite for W256 carcinomas. The lipid peroxidation in the stromatas of the tumours could be significantly reduced. Zarkovic sees in the anit-oxidants an effective substance to combat tumours [103] and proved also their effectiveness (especially of clinoptilolite) already in the formation of tumours [102].

Clinoptilolite has shown an excellent capability of use in cancer therapy to support convalescence, to increase the tolerance to chemo and radiation therapy and especially in the neutralisation of side effects of the therapy (esp. loss of appetite) [18,19].

Finally natural clinoptilolite could serve as a new adjuvant in anticancer therapy. Such treatment of mice and dogs suffering from a variety of tumor types led to improvement in the overall health status, a prolonged life-span, and a decrease in tumor size. Local application of clinoptilolite to skin cancers of dogs effectively reduced tumor formation and growth. In vitro tissue culture studies showed that finely ground clinoptilolite inhibits protein kinase B (c-Act), induces expression of p21 WAF1/CIP1 and p37KIP1 tumor suppressor proteins, and blocks cell growth in several cancer cell lines. Since previous studies have indicated that exposure of cells to silicate particles leads to activation of MAPK protein kinase C, and stress-activated protein kinases/JNK, [221] it was interesting to further analyze whether clinoptilolite treatment also affects mitogenic and survival signaling pathways in tumor cell models.

The most significant results were detected measuring the activity of Akt protein in tumor cells in vitro. Akt, or protein kinase B, has been recently shown to mediate survival signals down-stream of phosphoinositide-3 kinase by phosphorylating Bad proteins [222]. An increase in Akt phosphorylation was observed in response to serum, EGF, or insulin treatment.

The addition of a clinoptilolite-pretreated medium containing 10% FBS to the cells decreased Akt phosphorylation in comparison to the cells treated with only serum containing media. The addition of growth factors EGF and PDGF restored cell activity. Determination of the activity of Act at various times after the addition of clinoptilolite-pretreated medium with 10% FBS showed a slight decrease in pAkt level after 5 minutes. This decrease was more pronounced after 30 and 60 minutes of treatment. However, the addition of clinoptilolite pretreated medium without serum to the cells increased activity of Akt compared only to the serum-starved cells. Combined overnight treatment of the cells with EGF and clinoptilolite-pretreated medium decreased Act activity, indicating that inhibition of Act might be linked to clinoptilolite inhibition of the EGF-triggered pathways. MAP kinase (MAPK) activity was increased temporarily in serum-starved cells treated with clinoptilolite. In contrast, addition of clinoptilolite-pretreated medium plus 10% serum slightly decreased MAPK activity compared to serum-treated cells or cells incubated only with clinoptilolite-pretreated medium. Media pretreated with clinoptilolite added to the cells either alone or in combination with serum caused no change in JNK activity.

Inhibition of cell growth was due to programmed cell death, i.e. apoptosis. DNA fragments isolated from zeolite-treated cervical carcinoma cells (HeLa) exhibited significant degradation in comparison to DNA from untreated cells.

The removal of toxic substances from the body is one of the most efficient ways to protect against cancer.

Proliferation of Tumor Cell Lines in Vitro
Studies performed in tissue culture in vitro indicate that natural clinoptilolite treatment affects proliferation and survival of several cancer cell lines of human origin [222]. Addition of clinoptilolite inhibited cell proliferation in a concentration-dependent manner, in part due to induction of inhibitors of cycline dependent kinases, inhibition of B/Akt expression and induction of programmed cell death [222]. The growth of HeLa (cervical carcinoma), CaCo-2, HT-29, MCF-7 and SKBR-3 (mammary carcinomas) and mouse fibrosarcoma cells after 3 days of treatment was significantly inhibited with a dose of 50 mg/mL. The growth of normal fibroblasts was slightly stimulated. Similar results were observed measuring 3H-thymidine incorporation assay in the presence of 10% fetal bovine serum in mouse fibrosarcoma cells

Tumor Growth in Vivo
The range of effects on tumor growth in vivo are diverse, ranging from negative antitumor response, to normalization of biochemical parameters, prolongation of life span, and decrease in tumor size. The best results in animal models were observed in the treatment of skin cancer in dogs, suggesting that adsorption of some active components is responsible for clinoptilolite activity (direct contact action) [222].

Clinoptilolite, administered by gastric intubation to mice injected with melanoma cells, significantly reduced the number of melanoma metastases. In mice fed clinoptilolite for 28 days, the concentration of lipid-bound sialic acid in serum was increased, but lipid peroxidation in liver was decreased. The lymphocytes from lymph nodes of these mice provoked significantly higher "allogeneic" graft-versus-host reaction. After i.p. application of clinoptilolite, the number of peritoneal macrophages, as well as their production of superoxide anion, was increased. However, nitrite oxide generation was totally abolished. At the same time, translocation of p65 (NFkB subunit) to the nucleus of splenic cells was observed [223].

Subsequent studies were performed on murine transplantable tumors, melanoma B 16, and three different types of mammary carcinomas [222]. Tumor growth was significantly inhibited in animals suffering from anaplastic mammary carcinoma in groups of mice fed with food supplemented with clinoptilolite starting from 15 days prior to tumor transplantation until the animal's death, and animals fed with zeolite from the day of tumor transplantation until the animal's death. However there was no difference in mice survival among the control and zeolite treated groups. There was also no effect of clinoptilolite on two mammary carcinomas which histologically differed from the previous.

Mice bearing melanoma B16 were fed clinoptilolite for 30 days, five times per day. Tumor volume was markedly lower in 5 of 80 mice. Despite the fact that the tumors started to grow rapidly after therapy with clinoptilolite was discontinued (between days 30 and 60 after tumor transplantation), the mice lived statistically much longer when treated with 200 and 150 mg clinoptilolite than did the control animals [222].

Interesting results have been obtained with dogs [222]. Of 22 dogs suffering from various kinds of spontaneous tumors and treated with clinoptilolite, 14 responded to therapy, i.e. the tumor disappeared completely or the tumor size was significantly reduced. Three dogs had prostate tumors; one of these

was studied via ultrasound and found to also have a prostate cyst. This dog was conspicuously quiet, without appetite, and lethargic prior to treatment. When conventional therapies did not work, clinoptilolite therapy was started. After just 2 days of treatment the dog became active; on the third day it began eating normally, and on the fourth day the dog urinated normally. On day 10 the cyst and the tumor were reduced in size, and after 1 month they had disappeared completely. Although the prostate became only insignificantly smaller, the dog showed no signs of illness. Furthermore, the very high pretherapy serum values for aspartate aminotransferase (497 µM/L) and alanine aminotransferase (433 µM/L) decreased after 1 month of clinoptilolite therapy to normal levels (16 and 43 µM/L), and remained in the normal range for the entire observation period (5 months).

In addition to the effect of clinoptilolite on the primary disease, all dogs responded to zeolite therapy in a positive way. After about 7 days they displayed general constitutional and behavioral improvement that lasted even after therapy was discontinued. The same was observed for some of the haematological and serum clinical parameters measured before and after therapy. Hematocrit decreased to the normal range in one case, very high total serum bilirubin values fell to the normal range in two cases, and serum urea concentration changes were noted in another two cases. Elevated pretherapy values of aminotransferase, alanine aminotransferase, and alkaline leukocyte phosphatase all normalized after therapy was started in most cases [222].

6. SPORT

Due to Timo Vuorimaa [245] the energy delivery in middle and long distances is based on oxygen dependent metabolism. He claims as follows:
”According to the "Cardiovascular / Anaerobic model", named and criticized by Noakes (2001), the performance capacity of human muscles is dependent on the continuous delivery of energy in the form of ATP. The utilization and production of ATP are delicately balanced, although in athletic performances the energy needs of the working muscles may increase dramatically, e.g. during middle distance running over 1000-fold in a couple of seconds (Newsholme 1978, Bangsbo et al. 1990).

The most important biochemical processes producing ATP in human cells are oxygen independent glycolysis of carbohydrates and the aerobic metabolic pathways for the metabolism of carbohydrates and free fatty acids (the citric acid cycle, beta-oxidation and the respiratory chain). The relative importance of these processes differs from tissue to tissue and depends on the functional and nutritional state of the body. The choice of fuel (carbohydrates vs. free fatty acids) and the amount needed depend on the type and duration of muscle work (Newsholme 1976, Bangsbo et al. 1990).

It is well known that in prolonged athletic performances such as middle and long distance running ATP is produced mostly by oxygen-dependent metabolism in the mitochondria and that the performance is related to a great extent on the oxygen supply to these organs (e.g. Bassett and Howley 1997). On the basis of the early findings of Hill and Lupton (1923), it was long accepted that oxygen consumption rises as an exponential function of running speed and that anaerobic metabolism begins after the athlete achieves either the absolute V02.. or an individual V02 plateau at a certain running speed. Later, the role of oxygen-depended metabolism in prolonged exercises has been more critically discussed (e.g. Noakes 2001). On one hand, it is well documented that hypoxia develops in active muscles during an intensive exercise and causes fatigue. Based on that, and agreeing with Hill and Lupton (1923), many scientists have suggested that it is the V02max, which mainly limits the performance in prolonged muscle work as endurance running (Costill et al. 1973, Foster et al. 1978, Davies and Thomson 1979, Joyner 1991, Basset and Howley 1997). On the other hand, and especially in the case of endurance running, it is suggested that the maximum achieved work rate rather than the V02max is the best predictor of running potential (Scrimgeour et al. 1986, Lacour et al. 1990, Padilla

et al. 1992, Yoshida et al. 1993, Grant et al. 1997). Recently, it has been shown that the lowest velocity by which V02max can be achieved (the velocity associated with V02max) and further the time to exhaustion at this velocity are good predictors of performance in elite long distance runners (Billat et al. 1994, 1996, 1999). Especially on longer distances and in athletes with similar V02max values, the fractional utilization of V02max (%VO2max) and/or the lactate or respiratory compensation (ventilatory) thresholds measured in the laboratory (Costill et al. 1973, Farrell et al. 1979, Aunola and Rusko 1986), are suggested to relate with prolonged running performance (Costill et al. 1973, Farrell et al. 1979, Kumagai et al. 1982, Tanaka and Matsuura 1984, Noakes et al. 1990). Further, factors related with running economy have been linked to endurance running performance (Conley and Krahenbuhl 1980, Morgan et al. 1989a) especially in high level runners and with similar V02max values." And:

"During acute physical exercise large amounts of oxygen are inhaled into the human body. Oxygen consumption in the working peripheral skeletal muscle tissue may increase even 20-fold during intensive endurance exercising (Brooks and Fahey 1984). It is well known that prolonged aerobic training has many positive effects on human cardiorespiratory function and lipid metabolism, e.g. a reduction in the level of plasma triglyceride and an increase in the level of HDL cholesterol (Durstine and Haskell 1994). However, there is also strong evidence that the pro-oxidants released during a single bout of heavy and exhausting exercise may cause oxidative stress (Davies et al. 1982, Jenkins 1988) and harm various biological structures (Dillard et al. 1978, Del Maestro 1980, Davies et al. 1982, Brooks and Fahey 1984).

The magnitude of oxidative damage may be related to the power of the pro-oxidant attack (intensity and duration of physical exercise) and the capacity of the individual exerciser's antioxidant defence system (Davies et al. 1982, Halliwell 1994, Haramäki and Packer 1994, Kujala et al. 1995). It has been suggested that oxidative stress associated with exercise is better tolerated by trained subjects working at moderate intensity and not to exhaustion (Alessio 1993). Direct measurement of free radical signals can be made by electron spin resonance and indirect measures include e.g. mitochondria) membrane damage, conjugated dienes, hydroperoxides, thiobarbituric acid reactive substances, short chain hydrocarbons, and oxidized nucleosides (Alessio 1993)."

However intense physical performance may lead to increased levels of oxidative stress and oxidative damage to the body, therefore limitation of free radicals in the blood, prevention or at least reduction of oxidative stress is a goal.

6.1. Health promoting vs. Health threat

It is well known that sport has positive influences on the progress of many diseases, for example osteoporosis, diabetes, cardio-vascular diseases or arthrosis. A Finnish study performed on 104 mostly sedentary people (124) showed that the percentage of low density lipoproteins or LDL that plays a direct role in the development of arteriosclerosis could be significantly reduced by a 10-month programme of light sports (3 times a week cycling, walking and dancing). Covas et al. found that the amount and intensity of leisure sport activities had a direct positive influence on biomarkers for oxidative stress by women [125]. Moderate training can also have a positive influence on the blood lipid profile in humans [126]. Sporting hobbies can have a positive influence on dyslipidaemia, the cardio-respiratory fitness, can possibly reduce lipid peroxidation by otherwise healthy patients with diabetes type 1, can reduce the risk of metabolic syndrome and therefore be preventative against chronic and progressive diseases like diabetes and arteriosclerosis [32].

Especially in this area Panaceo can provide a contribution to therapy support, by intervening in the responsible parameters – especially the lipid peroxidation and therefore reducing the negative effects

and supporting the therapy success. For the patients this means the minimal risk of a sub-optimal training and a higher possibility of a positive therapy process as a result.

An intensive physical exertion manifests itself in general in an increase of antioxidative enzymes which are: superoxide dismutase (SOD), glutathione peroxidase (GPx), haemooxygenase (HO-1) and heat schocl protein (HSP70) [128,129]. Numerous studies have shown that intensive or improperly performed muscle training causes oxidative stress and produces poisonous oxidated substances. Different mechanisms are responsible for this: the increase in oxygen burning during physical exertion, muscular hyperthermia, spontaneous oxidation of the catecholamines or lactic acid, increase in the Ubichinon turnover , ocurrence of local ischaemia and reperfusion (especially in the intestines) and appearance of inflammation from the high activation of white blood cells. The consequences of oxidative stress for athletes are numerous: muscle damage, cramps [131], increase in tiredness (asthenia), poor recuperation phase.

6.2. Lactate – energy source, Indicator for training level or simply a toxin?

Especially pronounced physical effort produces a significant increase in lactate in blood, that results form the frequency and recruiting of mainly intermediary and fast muscle fibres. Especially in competitive athletes during the exertion period 30 to 150 seconds as a result of the anaerobic glycolysis it can come to high muscle and blood acidosis due to the increase in lactate As the trained athlete, especially those that have trained in the anaerobic area, is accustomed to producing these acidoses and has because of the training a higher acidosis tolerance these high lactate acidoses are nonhazardous as opposed to clinical diseases where they can occur.

Apart from physical exertion (muscle work) it can come to an increase in lactate also during operations, heart insufficiency, diabetes mellitus, myopathy, and all conditions where there is a reduced oxygen supply (hypoxia). The symptoms are compensatory hyperventilation (deep breathing), nausea, vomiting and in pronounced cases even shock symptoms, lactate acidotic coma and renal failure. The direct relationship of the lactate acidosis as a cause of the stress-induced hyperventilation at the respiratory compensation point was first described by Meyer et al [22].

The underlying study of the effect of Panaceo in keeping the lactate level low during physical stress is a randomised, placebo controlled, double blind study with 24 test persons. After a week of 3 x 3 intake of Panaceo Sport capsules and the same stress on the treadmill (10 km/h) an average reduction of the capillary measured lactate value of 24.2% was measured and after two weeks of intake a 46.9% reduced lactate concentration was measured. At a speed of 14 km/h a 15.9% reduction in lactate concentration was shown after one week of intake and after two weeks 23.3%. The control group showed no significant change to the lactate level, in fact on average there was a discrete increase [21].

6.3. Mechanism of action

In the aerobic range energy is provided by aerobic metabolism with a minimal lactate creation, whereby glucose is decomposed to pyruvate which is then in further steps (acetyl coenzyme A) channelled into the citric acid cycle. At the same time lactate hydrogenase (LDH) transfers hydrogen (H) from reduced nicotinic acid amidadenine-dinucleotide (NADH) to pyruvat whereby lactate is formed. The minimal lactate produced under aerobic conditions is also metabolised into the citric acid cycle as carbohydrate metabolite and into the respiratory chain releasing energy creating water (H2O) and carbon dioxide (CO2) or if there is energy surplus back to glucose and further to build glycogen (glycognesis) [57].

Natural clinoptilolite reduces the damages to biological structures by bonding heavy metals and neutralising free radicals (e.g. lipid peroxidation to the cell membranes, oxidation of the DNA bases) in the gastrointestinal tract. These effects have an impact on the whole organism. A reduction of damages and neutralisation of free radicals produces a reduction in energy in the whole organism that otherwise would be used to repair the damaged biological structures and therefore can be used for other purposes. The correlation between the selectivity of clinoptilolite and free energy in diluted solutions was examined by Torres and Gubulin [79]. The energy savings mentioned result in a reduction in use of oxygen for the provision of energy that would otherwise be used for repair respectively biosynthesis (esp. phospolipids of the cell membranes) and can now be used for aerobic metabolic processes.

It can therefore be assumed that under physical stress an improved oxidative metabolic situation could be given whereby positive effects on the interaction in aerobic/anaerobic metabolism under high stress intensity could be given. This effect can be measured objectively with the lactate value and a shift in the lactate curve.

The anti-oxidative effect of Panaceo clinoptilolite may lead to significantly reduced ROS level and prevent oxidative damage to the organism, therefore supports the positive effect of sports-activities and prevents or at least reduces possible negative effect of intense or false physical performance that can be measured by a decreased blood lactate level and decreased ROS level.

7. LOCAL APPLICATION AS SKIN AND WOUND POWDER

7.1. Absorption of Exsudates

Due to its micropores and enormous surface and hydrophilicity zeolite is used for the absorption of exsudates in the wound area. Zeolite activates the thrombocytes (platelets) and encourages them to release PDGFF-AA which in turn stimulates the fibroblasts and therefore contributes to a quick healing. Apart from that with the addition of zeolite the recalcification time (R time) in the thromboelastgramme (a coagulation test) could be significantly reduced in comparison to unprepared samples, which proves the haemostatic effect of zeolite [104].

7.2. Promotion of wound healing

Also helpful for use in the wound area is zeolite's high adsorption capability of ammonium which is increasingly produced just when cells are decomposing (as in the area of injured or damaged skin) [20].

Zeolite hemostat (ZH) was proven as an effective agent for control of severe bleeding, and it is currently being used by the US troops in the battlefield. ZH causes an exothermic reaction on application, which theoretically can be decreased by altering its chemical composition or changing its physical properties. However, the effect of these alterations on the hemostatic efficacy is unknown. We tested modified zeolites and a chitosan based dressing against controls in a swine model of battlefield injury.

A complex groin injury was created in 60 swine (40-55 kg). This included semi-transection of the proximal thigh (level of inguinal ligament), and complete division of the femoral artery and vein. After 3 minutes, the animals were assigned to (1) no dressing (ND), (2) standard dressing (SD), (3-5)

SD + chemically modified ZHs, where calcium was substituted with sodium (Na), barium (Ba), or silver (Ag), respectively, (6) SD + physically modified ZH, where "beads" were packaged in a fabric bag, (7) SD + chitosan based dressing (CD). Resuscitation was started 15 minutes after application of dressing (500 mL of 6% hetastarch over 30 minutes). Survival for 180 minutes was the primary endpoint for this study. In addition, blood loss, wound temperatures, and histologic tissue damage were recorded.

Mortality in the group that was treated with the application of bagged ZH was 10% versus 100% in the no dressing group and 50% in the SD group ($p < 0.05$ vs. ND and SD groups). The Na ZH group had a mortality rate of 43%, whereas application of Ba and Ag substituted zeolites, and CD were associated with a mortality rate of 25%. Ionic substitution of zeolite decreased the in vivo temperature peak by 5 to 10[degrees]C. No histologic evidence of tissue necrosis was noted in this experiment.

Conclusions: The use of zeolite hemostat can control hemorrhage and dramatically reduce mortality from a lethal groin wound. Modifications of zeolite hemostat can decrease the exothermic reaction and attenuate tissue damage.

Zeolites have become a valuable medical resource. QuickClot, a product not available to the public at this point, has saved many lives with its blood coagulatin properties. Emergency personnel and the military have it readily available. Heavy bleeding that occurs when femoral arteries are severed, can be stopped by ground up and sterilized zeolite.

QuikClot is a brand of hemostatic agents that is manufactured by Z-Medica Corporation. The original QuikClot was a granular product that was be poured directly on wounds to stop bleeding. It works by adsorbing water from the blood, concentrating the clotting factors, activating platelets, and promoting steps in the coagulation cascade. It is composed of zeolite, a molecular sieve that traps molecules in a molecular "cage" and holding the trapped species by forming hydrogen bonds. The bond formation generates heat, which has been a drawback to the original QuikClot product. Newer versions of the product are partially prehydrated and generate less heat, at a slight cost in clotting speed.[206]

Using zeolite as a hemostatic agent was discovered by Frank Hursey (who cofounded Z-Medica) in 1984.[207] Following the September 11th attacks, the U.S. Navy conducted a test comparing new technologies to stop bleeding. QuikClot performed the best in these tests, which have been replicated many times by many different groups.[208, 209] Following this testing, the United States Marine Corps deployed the product in Afghanistan and Iraq. QuikClot is now carried by the Navy, Coast Guard, Army, and Air Force in addition to the Marines. It is now standard issue for several police departments [210]. There is also a consumer version for use by athletes and people at risk for bleeding. Another QuikClot product provides both the hemostatic effect and also antimicrobial properties of ionic silver.

The product is now used routinely to save lives, some cases have been published [211].
QuikClot can be seen in the movie Shooter used by the main character to curtail bleeding caused by two gunshot wounds.

Limitations: In order to be effective, QuikClot must be applied to the source of the bleeding, the torn blood vessel itself. This is often accessible in an open laceration, but may be deeply buried and inaccessible in case of a puncture or gunshot wound. Also, foreign material or accumulated blood may have to be washed out to provide access to the bleeding vessel.

With the original formulation, if large amounts of blood and QuikClot are combined (particularly if a QuickClot is rapidly applied to less than half its volume in blood [212]), the generated heat can be enough to cause burns. This may still be preferable to continued blood loss [210].

The granular form is awkward to apply in windy environments, requires that the wound be facing upward, and is difficult to combine with direct pressure. A sponge form (QuikClot ACS) has been developed to address this concern [206].

Techniques for better hemorrhage control after injury could change outcome. We have previously shown that a zeolite mineral hemostatic agent (ZH) can control aggressive bleeding through adsorption of water, which is an exothermic process. Increasing the residual moisture content (RM) of ZH can theoretically decrease heat generation, but its effect on the hemostatic properties is unknown. We tested ZH with increasing RM against controls and other hemostatic agents in a swine model of battlefield injury. METHODS: A complex groin injury was created in 72 swine (37 +/- 0.8 kg). This included semitransection of the proximal thigh and complete division of the femoral artery and vein. After 3 minutes, the animals were randomized to 1 of 10 groups: group 1, no dressing (ND); group 2, standard dressing (SD); group 3, SD + 3.5 oz ZH with 1% RM (1% ZH); group 4, SD + 3.5 oz ZH with 4% RM (4% ZH); group 5, SD + 2 oz ZH with 1% RM (1% ZH 2oz); group 6, SD + 3.5 oz ZH with 8% RM (8% ZH); group 7, SD + chitosan-based hemostat, HemCon (HC); group 8, SD + 3.5 oz nonzeolite mineral hemostat, Quick Relief (NZH); group 9, SD + bovine clotting factors-based hemostat, Fast Act (FA); and group 10, SD + 30 g of starch-based hemostat, TraumaDex (TDex). Resuscitation (500 mL of Hespan over 30 minutes) was started 15 minutes after injury and hemodynamic monitoring was performed for 180 minutes. Primary endpoints were survival for 180 minutes and blood loss. In addition, maximum wound temperatures were recorded, and histologic damage to artery, vein, nerve, and muscle was documented. RESULTS: Use of 1% ZH decreased blood loss and reduced mortality to 0% ($p < 0.05$). Increasing the RM adversely affected efficacy without any significant decrease in wound temperatures. Minimal histologic tissue damage was seen with ZH independent of the percentage of RM.

Conclusion: The use of zeolite hemostatic agent (1% residual moisture, 3.5 oz) can control hemorrhage and dramatically reduce mortality from a lethal groin wound [214].

7.3. Ulcers, herpes

Gasser observed a quick, painless and reaction less wound healing when using Panaceo in over 100 patients over 5 years for badly healing wounds, venous and arterial calf ulcers and herpes labialis and genitals. There was no intolerance in any of the cases even when used the genital area 106].

There are some scientific evidence that zeolites have antiviral properties, that open a possibility of therapeutical application of particularly clinoptilolite either locally (skin) against herpes virus infections or orally in cases of adenovirus infections. However, the inhibitory effect of viral proliferation was observed with high concentration of micronised clinoptilolite (over 12 mg/ml) which makes the clinical applications and the dose-response effect difficult to establish. Fortunately, clinoptilolite could be used in purification of drinking water from different viral particles without concern of concentration of clinoptilolite for application. The mechanisms of action of clinoptilolite upon different types of viruses are probably non-specific which makes it more interesting than conventional antiviral drug. Such inactivation of viral particles by clinoptilolite would be extremely interestinh for viruses that infect the digestive tract such as enteroviruses, and because clinoptilolite can be orally administered without toxicity it could be used for therapeutic.

Herpesviruses are able to establish life-long latency after primary infection that can be reactivated, especially in immunocompromised transplant recipients and patients with AIDS. Generally, herpesvirus infections have been treated successfully with systemic administration of acyclovir. However, drug resistance variants emerge after long-term treatment, which leads to treatment failures.

This is why new efficient and inexpensive potential drugs such as clinoptilolite could be helpful to inhibit, if not eradicate, viral infections. Additionally, clinoptilolite could be administered locally on skin as cream or gel in order to inhibit recurrent labial and genital herpesvirus infections that are often physiologically and physically very painful.

The adsorption capacity of clinoptilolite and mordenite has been proved to be higher than 94% for virions of bovine rotavirus and coronavirus, although infectivity level of zeolite-virus complex seems to remain unchanged. Interactions among virions and the outer surface of adsorbent particles have been proposed, since the former has dimensions considerably larger (60-80 nm and 60-220 nm for rota- and coronavirus particles, respectively) than the entry channels of the aforementioned zeolites. [215]

7.4. Burns

Bedrica et al described the treatment of a five year old Cocker Spaniel bitch and her two puppies that received numerous burns from a fire caused by a gas explosion in the flat. The effect of natural zeolite clinoptilolite on the healing of the burn wounds was studied during normal therapy. Blood was removed from the bitch and the puppies for a haemogram and for several biochemical blood analyses. It was determined that the creatinine and urea values which were far above the physiological levels before the use of clinoptilolite were after a one week treatment with clinoptilolite back to normal. Based on the case presented here it could be proved that the use of clinoptilolite simultaneously with the normal therapy for burns accelerated the recovery of the animals and is capable of bringing about a complete healing even considering the fact that 50% of the bitch's skin surface was affected. Liver and kidney damage could also be avoided with the use of clinoptilolite. [107]

7.5. Acne

Thoma observed a very quick improvement of acne with a simultaneous local and oral application in skin patients, especially acne patients who had already gone through all clinical methods. [108] Zechner was able to observe, especially in girls between 15 and 25, a significant improvement of the clinical picture with a likewise simultaneous oral and local application of Panaceo zeolite. Gunzer determined an almost complete disappearance of acne with simultaneous local and oral application [110].

8. DOSAGE RECOMMENDATIONS

Always take with a glass water at or immediately after meals.

Clinical use for chemo and radiation therapy
In the first 3 weeks 9-12 capsules of Panaceo MED tablets daily in combination with 3 measuring spoons of Panaceo MED powder. Afterwards 6-9 capsules daily and a measuring spoon of Panaceo MED powder. Do not take for one day before, during and after the chemo or radiation therapy. The intake should be continued after successful healing of the disease at least as a cure for several months per year.

Bone density, osteoporosis, irritable bowel syndrome, detoxification of gastrointestinal tract
2-3 times daily 3 capsules
Panaceo MED in tablet form: 2-3 times daily 3 tablets

Panaceo MED in powder form: 1-3 times daily 1 measuring spoon
Duration of intake: The intake should be continuous for osteoporosis as an interruption of the intake would result in a renewal of the deterioration in bone density. For irritable bowel syndrome and detoxification the intake should be continued at least as a cure for several months a year even after an improvement in the symptoms.

Eyes
2-3 times daily 3ea capsules Panaceo Focus: Duration of intake: At least as a cure for several months (3-6) times a year.

Memory
2-3 times daily 3ea capsules Panaceo Smart. Duration of intake: At least as a cure for several months (3-6) times a year.

Anti-oxidants
2-3 times daily 3ea capsules Panaceo OPC+C. Duration of intake: At least as a cure for several months (3-6) times a year.

Sport
2-3 times daily 3ea capsules Panaceo Sport. As an alternative 6 capsules before and after sport competitions. During longer periods of competition an additional 2 capsules can be taken each hour. In addition it often makes sense to add a measuring spoon of Panaceo powder to the water bottle but always shake well before drinking so that the clinoptilolite does not remain at the bottom. The intake should be started at least two weeks before the competition. Preferably the intake should be continued during the regeneration phase.

Skin and wound powder
If required cover the skin or small wounds with some powder up to 5 times daily until completely healed.

9. LIST OF LITERATURE

The complete list of literature can be seen at Panaceo International Active Mineral Production GmbH. To protect intellectual property this list of literature will not be published.

10. APPENDIX: STATEMENTS AND REVIEWS

Prim. Dr. Wolfgang Thoma, Medical Director of Privatklinik Villach, November 2005

We have been using this agent for approximately 5 years – on approx 500 patients. We chose different clinical patterns, above all very sick patients i.e. patients with hepatitis C, carcinoma patients, rheumatologic patients but also patients with pronounced acne where Panaceo was applied locally and have had a very high percentage – so high that I as orthodox medical practitioner have used for the last 5 years – of general significant improvement. The general condition of cancer patients improved within a short period of time especially the appetite and physical fitness. More success was determined with breast, lung and ovarian cancer and less with gastric and pancreatic cancer. In the last two mentioned forms of cancer the response to the medical product was clearly worse. The reason could not be determined as only an observation of application was performed and not a clinical study. In skin patients – especially acne patients who had already gone through all clinical methods - a very quick improvement to the acne was observed. The advantage of this medical product is that it works within one week and if during this period no improvement occurs then it can be said that the indication was not suited for the patient.

OA Dr. Elisabeth Zechner, Internal medicine specialist, November 2005

I have treated patients, amongst others also my mother, with this medical product for many years and this was up until now the most astounding result: My mother suffers from an ovarian carcinoma and had to have chemotherapy several times so far. The first two chemotherapies were very stressful for her due to the usual side effects. When I learned about zeolite – the content of Panaceo – I used it on her and the results were astonishing: my mother had hardly any side effects and tolerated the chemotherapy well, her general well being improved and she no longer suffered loss of appetite – all of the side effects were significantly reduced. For this reason I started to use this medical product on other patients and could very often observe the same results. I gathered experience with not only cancer patients that had had chemotherapy but also with those who had other medicament therapy – with all of them an improvement to their standard of living could achieved. We have of course also tired to determine if healing is possible – until now this could not be confirmed by us. But a protraction of the disease respectively a protraction of the progression of the disease could in any case be achieved with Panaceo. For example in my mother's case the disease was diagnosed at such a late stage that all my colleagues said that she would die within one year. Thereupon we administered this medical product with the ingredient zeolite – she thus tolerated the chemotherapies well and is till alive today with a very good life quality. This happened 9 years ago!

We have also gained experience with young acne patients, especially with girls aged 15 to 25. They came repeatedly with pronounced acne in the face and on the back and we treated these patients with zeolite powder both locally and orally i.e. the patients swallowed the capsules and the powder. In approx. 70% a significant improvement in the clinical pattern was observed. We also had a lot of experience with patients with open legs i.e. with ulcer formations on the legs caused by circulation damage or by nerve damage. We applied the zeolite powder locally to the patients and in addition they swallowed it and therefore an improvement in the condition could be achieved. Small ulcers were healed and that in my opinion is a great success as the patients were not subject to severe medication but a natural product was sufficient. My explanation for the effect of zeolites is that a patient with the above diseases – i.e. chronic diseases – an increased level of free radicals exists and zeolite is a so-called radical catcher. We could observe in the laboratory that the radical level sunk significantly with the intake of zeolite. Above all in patients with carcinomas – i.e. cancer patients - a high radical level can very often be found. It is also very important to me that patients that are considered to be "healed" continue to take zeolite. All of our patients that leave the hospital and primarily received zeolite from us subsequently continue to take the product and we continually control the radical level. The Maca is actually responsible for the patients well-being – this is correlated to the radical level - this could be observed in the last few years.

Dr. Claudia Gunzer, Laboratory Director of Privatklinik Villach, November 2005

A patient that continually returns because she suffers from acne. Her free radical level was established months ago and was prescribed the medical product Panaceo both orally and for external application. You can see how her face has become smoother – the acne has almost vanished. If the patient becomes neglectful and does not take the tablets or apply the powder the acne the acne becomes stronger again. As soon as the medical product is taken regularly again and the face is treated with the powder you can see immediately after the success.

We measure the free radical levels in blood of hundreds of patients with the idea of helping the patient to a better general condition. Some of them are carcinoma patients who have a much lower radical level thanks to the effect of Panaceo and who fell physically better and above all fitter. Also, it can be observed in patients with hepatitis – especially hepatitis C – that they have a significantly better physical general condition from the intake of this medial product.

Dr. med. univ. Thomas Scheiring, Director of Sportmed-Telfs , two time Ironman and six time Ötztalmarathon finisher

"In our own studies during the application observation to some extent astounding improvements of (already endurance trained) participants were observed. In the full load-steady-state test (watt performance from previous level test at 4mmol lactate) not only lower lactate levels were measured with Panaceo but also the times up to load break off were increased by up to 25% in individual cases. Test persons with higher lactate at the beginning profited especially form the Panaceo intake.

In other words: All competitive athletes that do not take Panaceo during competition forgo a possible doping free significant increase in performance."