



## **Information for healthcare professionals 2016**

### **PMA-Zeolite® (PMA: Panaceo-Micro-Activation)**

**Study summary and explanations on  
the mechanism of action and intended main effect**

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## **Constant overload makes our body sick!**

**According to the World Health Organisation (WHO), despite considerable progress in environment and health in recent decades, environmental toxins are still responsible for one quarter of all illnesses and deaths in the European Region.<sup>1</sup>**

Although the health consciousness of the population is steadily growing, at the same time increasingly more people are suffering from the new lifestyle diseases of the western world. Humans are thus strained by rising fatigue, digestive problems, headaches or insomnia, diseases of the gastrointestinal tract, liver and kidney diseases, skin diseases, respiratory diseases, and diseases of the central nervous system. The lack of a uniform disease pattern makes the search for specific triggers difficult. The causes are often diverse, and the processes are often insidious.<sup>2</sup>

In recent years, it has become evident that diseases caused by the chronic accumulation of environmental toxins (especially heavy metals) occur more frequently than previously thought.<sup>3</sup> Low concentrations of these contaminants (such as cadmium or lead) can accumulate in the soil and subsequently in aquatic and terrestrial food chains.<sup>4</sup> Accordingly, as documented by the European Rapid Alert System for Food and Feed (RASFF)<sup>5</sup>, high levels of environmental contaminants are continually found in our food.

“How toxic is my food?” This question was addressed by food profilers in the journal “Welt der Wunder, May 2015 Edition”. The answers were startling.<sup>6</sup> According to the University of Bergen, farmed salmon is one of the most toxic foods in the world.<sup>7</sup> In addition to farmed salmon, many other foodstuffs are overloaded with contaminants such as antibiotics, pesticides, and heavy metals. According to Food Watch, pesticide residues (among other things) can be found in animal feed. Through the consumption of animal products, these end up in the human food chain.<sup>8</sup> Despite the possible negative effect of pesticides on health and their persistence in the environment, the continued use can be explained by the pressure to produce enough affordable food for a population that has doubled since 1950. It should be added that, despite a doubling of the population, the area of arable land has increased by only 10%. Although the use of pesticides appears to be essential, according to Greenpeace, in the long term, it can negatively affect our environment and humans.<sup>9</sup>

According to environmental physician, Hans-Peter Hutter (in an interview with Martin Schriebl-Rümmele, environmental journalist)<sup>10</sup>, the largest environmental stresses are not visible. Because of the low attention they receive, they are all the more devastating. Research on the effects of environmental pollutants in the last 30 years has made it clear that these are far-reaching and diverse and can also influence human health.<sup>11</sup>

*Dealing with medications*

*Pesticides, herbicides, and the like*

*Air pollution*

*Unhealthy nutrition and more*

**In summary, the increase in air pollution (particulate pollution), the alarming number of contaminants (heavy metals, pesticides, fungicides, and herbicides) and synthetic additives (colours, flavours, and preservatives) in our foods, the use of medications and socially acceptable drugs (nicotine, alcohol, caffeine, and painkillers), and harmful substances in detergents, polishes, and cleaning products all put additional stress on our bodies. It is understandable that in addition to genetic disposition, the personal lifestyle and harmful environmental factors can insidiously contribute to lifestyle diseases.**

In order to prevent this, individuals can take measures to reduce or avoid risk factors as well as adopt a more health-conscious lifestyle. The results of a pioneering British human study involving more than 20,000 subjects clearly demonstrates the effects of a healthy lifestyle compared with an unhealthy one. Health behaviour was evaluated by combining four parameters (smoking/movement/alcohol consumption/nutrition). It was revealed that the difference in life expectancy between subjects with healthy and unhealthy lifestyles was 14 years.<sup>12</sup>

Because adjusting our lifestyles cannot eliminate all risk factors, **new approaches are required to support or relieve our natural protective mechanisms and detoxification capacity before our bodies reach their limits.**

### **PMA-Zeolite protects the body from unwanted substances**

**Through its proven pollutant binding effect in the gastrointestinal tract, PMA-Zeolite can contribute to the maintenance or acquisition of vitality, health, and well-being.**

“The main intended action of PMA-Zeolite is to reduce the additional daily stress by reducing direct exposure to contaminants, thereby eliminating the possible causes of increased intestinal wall permeability. Through the main intended mechanism of binding contaminants, PMA-Zeolite can support the gastrointestinal tract and the detoxification organs, especially the liver\*”.

\*) Extract from the evaluation report of the certifying body

If the intestines are healthy, the individual is healthy. This insight is as old as medicine itself. Even Hippocrates (Greek physicians, 300 BC) said: “The healthy gut is the root of all health”. Nowhere else in the body is there a more intensive contact with foreign substances than in the intestines. A powerful protective barrier is therefore “the first guardian” of our immune system and thus an essential prerequisite for a well-functioning metabolism.

**Protecting the intestinal barrier also involves strengthening the body's own defence system against undesirable substances and relieving the detoxification system.**

### **The intestinal wall - the protective barrier of our body**

As a result our daily confrontation with toxins from the environment, food, detergents, and cleaning agents as well as recreational drugs (nicotine, alcohol), our body must be highly adaptable. The gastrointestinal tract plays a particularly important role because this is the largest interface to the outside world. Up to 1 t of nutrients/year (adults) are transported through this “border barrier”. At the same time, the intestinal mucosa, which has a large surface area, provides an efficient barrier against the absorption of inadequately digested food particles, bacterial endotoxins, inorganic pollutants, and heavy metals.<sup>13</sup>

In addition to the essential barrier function, the intestinal mucosa/intestinal wall and the gut-associated lymphoid tissue (GALT) represent the main site of the immune system. Approximately 80% of all the body's immune cells are found in the intestinal mucosa. This means that the intestinal mucosa plays a central role in defence responses.<sup>14</sup> In this connection, the intestinal microbiome, which is composed of a large number ( $1 \times 10^{14}$ ) of micro-organisms, is essential for defence. It has therefore been the subject of numerous studies.<sup>15</sup>

### **Leaky gut syndrome**

The intestinal mucosa and the intestinal wall can become damaged (e.g. impaired or reduced intestinal flora, malnourishment, problems neutralising toxins, and dysbiosis) or even permeable through repeated

confrontations with various noxious substances from the environment, diet, and medication as well as stress and infection.<sup>16</sup> In the literature, the increased intestinal permeability is often used as a synonym for leaky gut syndrome.

The occurrence of leaky gut syndrome can be described as a loosening of the tight junctions (membrane proteins e.g. in the intestinal epithelium that form a para-cellular barrier and control molecular flow). Large molecular weight substances, foreign antigens, and bacteria can thereby diffuse through the intestinal epithelium and pass into the gut-associated lymphatic tissues and eventually into the bloodstream.<sup>18</sup>

The loss of the barrier function thus increases the risk of an uncontrolled influx of antigens into the lamina propria (i.e. layer of connective tissue) and ultimately into the circulation or the bloodstream. As a result, contaminants such as unwanted metabolic waste products or even bacteria can enter the bloodstream, thereby further overloading the detoxification system (i.e. the load exceeds the degradation rate) and inducing a permanent inflammation. This chronic disease process not only affects the immune system but nearly all organs. This can affect the entire body.

The initial symptoms of increased contaminant load of disorders of intestinal wall integrity can include non-specific symptoms such as a gradual drop in performance, allergies, fatigue and listlessness, difficulty concentrating, insomnia, or increased susceptibility to infections. Symptoms connected with leaky gut syndrome include **inflammatory irritable bowel**<sup>19</sup>, **auto-immune disorders**<sup>20</sup>, and **non-alcoholic fatty liver**<sup>21</sup>. Accordingly, an uncontrolled influx of antigens triggers local and systemic immune responses, which may lead to the development of serious diseases if they persist.

### **Leaky gut – development and consequences**

*Stress*

*Toxins*

*Food particles*

*Medications*

*Pathogens*

*Body malfunctions*

*GIT inflammation*

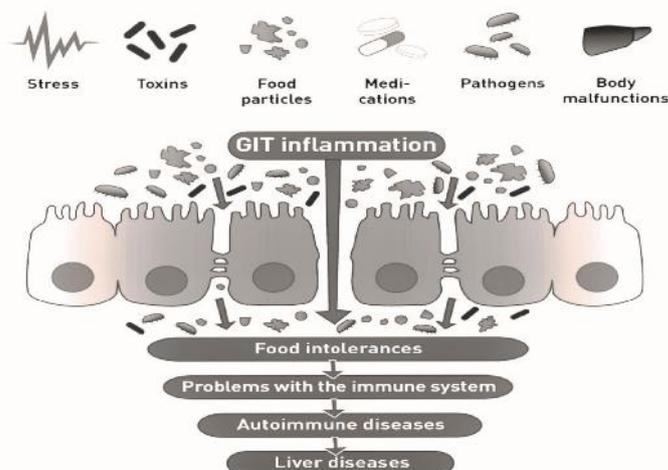
*Food intolerances*

*Problems with the immune system*

*Autoimmune diseases*

*Liver diseases*

### **Leaky gut – development and consequences**



**Figure 1:** Overview of the development and consequences of leaky gut syndrome<sup>17</sup>

## The intestinal barrier

Healthy intestinal barrier

**Gap junctions**

**Goblet cell**

**Tight junctions**

Impaired intestinal barrier

**Endotoxins in the blood**

Food and liquid → protection against deficits

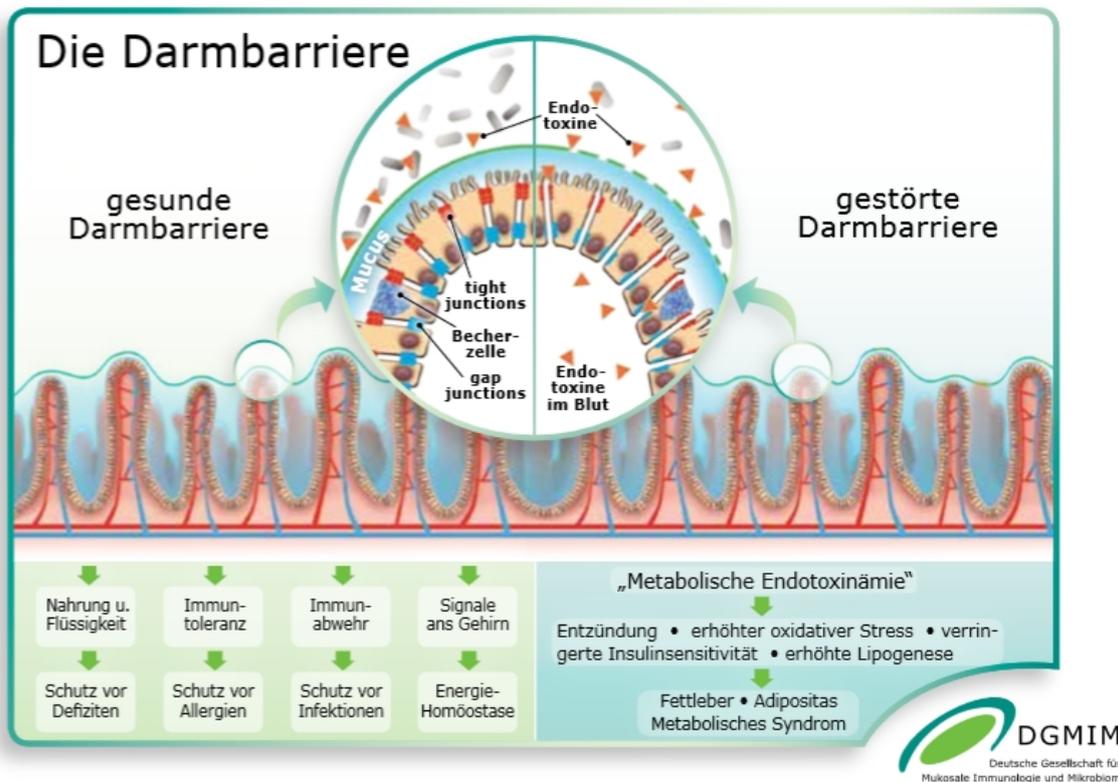
Immune tolerance → protection against allergies

Immune defence → protection against infections

Signals to the brain → energy homeostasis

"Metabolic endotoxemia" → Inflammation • increased oxidative stress • reduced insulin sensitivity •

Increased lipogenesis → fatty liver disease • obesity • metabolic syndrome



**Figure 2:** Illustration of healthy and damaged intestinal barrier including functions and the effects of malfunctions<sup>22</sup>

The figure from the German Society for Mucosal Immunology and Microbiome provides an overview of the effects of an overloaded gastrointestinal tract. The protection of intestinal health is therefore highly important for a functioning immune system. In any case, an overloaded gastrointestinal tract should be included as a possible cause for the above symptoms.

Through the absorption of contaminants and the strengthening of the intestinal wall barrier, the natural mineral PMA-Zeolite is a natural yet effective way to positively influence our health.

Panaceo products based on PMA-Zeolite are certified as medical products throughout Europe. Useful information about current research and development as well as the structure and mechanism of action of PMA-Zeolite is summarised below.

## Research and development

### Guiding principle

Continuous research and development is a key component of Panaceo. It affords the highest quality standards for a safe and effective medical product as well as the systematic documentation of the characteristics and application range of PMA-Zeolite.

Worldwide, there are around 200 different types of naturally occurring zeolite and synthetic zeolite (e.g. zeolite A). However, in order to ensure safe application, end consumers must realise that: zeolite  $\neq$  zeolite. Based on current knowledge, of all known types of zeolite, only natural zeolite-clinoptilolite is suitable for human application. As part of the selection and further processing, precise quality characteristics must be defined. These must include the clinoptilolite content, the mining area, and a careful mining method as well as strict examinations with regard to microbiological contamination, the occurrence of radio-nuclides, and heavy metal contamination.

In the course of further processing, using the specific PMA process technology (particle to particle collision using very high kinetic energy), essential characteristics of the defined natural mineral are optimised in terms of characteristic sorption and safety features such as the form, size, surface, and charge of the particles.

Panaceo is well aware of its leading role in the research, production, and optimisation of natural contaminant sorbents. For over 15 years, the company has been researching natural zeolite-clinoptilolite in cooperation with scientists and experts from renowned institutes and universities. Because research and development is a crucial element for certified medical products and the safety and efficacy of PMA-Zeolite have the highest priority, numerous studies (preclinical and clinical) have been commissioned.

Thanks to continuous research and development, PMA-Zeolite is both effective and safe – guaranteed, tested, and continually monitored.

**As a healthcare company, it is our vision to offer effective protection against the increasing exposure to contaminants, thereby allowing our consumers to regain or maintain their health.**

- ✓ Approval as a medical product (CE marking is a product qualification and a security feature)
- ✓ ISO certification EN ISO 13485
- ✓ European patents
- ✓ Continuous research and development in cooperation with renowned experts as well as European universities and institutes
- ✓ PMA process technology for a significant and measurable increase in effectiveness

**Table 1:** In summary, the following quality characteristics of Panaceo medical products based on PMA-Zeolite differ from non-certified zeolite products.

### Methodology of the study and proof of effectiveness

In order to comply with the regulations and requirements of a certified medical product and guarantee consumers the highest safety and efficacy, Panaceo Medical devices undergo the following phases during study planning and implementation:

#### 1. Safety

#### 2. Mechanism of action

#### 3. Operative hypotheses and proofs of efficacy

a. Intended main effect (clinical/Gold Standard)

b. Validation of secondary effects (basic research or application observations)

#### 1) Studies on product safety/toxicology

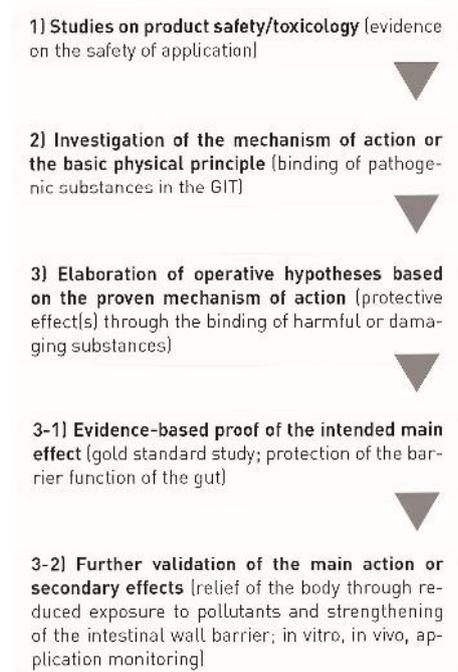
(evidence on the safety of application)

**2) Investigation of the mechanism of action or the basic physical principle** (binding of pathogenic substances in the GIT)

**3) Elaboration of operative hypotheses based on the proven mechanism of action** (protective effect(s) through the binding of harmful or damaging substances)

**3-1) Evidence-based proof of the intended main effect** (gold standard study; protection of the barrier function of the gut)

**3-2) Further validation of the main action or secondary effects** (relief of the body through reduced exposure to pollutants and strengthening of the intestinal wall barrier; *in vitro*, *in vivo*, application monitoring)



**Figure 3:** Representation of the evolutionary phases of the study planning and execution

**Product safety:**

Ongoing research activities represent an important basis for fulfilling the safety aspects of Class IIa certified medical products. The chemical and physical characterisation of the specific PMA-Zeolite is fundamental. The pH stability to acids and bases as well as temperature stability and the appropriate particle shape (round and no needle-shaped particles) should be demonstrated. According to ISO standard, recording of safety entails tests for cytotoxicity, sensitisation, and irritation. In addition to the tests required by the MPG, toxicological studies (sub-acute, acute, and chronic) as well as tests for genotoxicity and reproductive/developmental toxicity must be performed in order to ensure additional safety. The safety-relevant aspects were examined and evaluated by both the designated notified body as well as experts in the field.

Thanks to these tests (including expert reports), the safety of PMA-Zeolite for human use and the reach of efficacy of the gastrointestinal tract were clearly defined.

**Mechanism of action:**

Based on the clear evidence for safety, the mechanism of action was defined. With regard to the recognised detoxifying potential of zeolite-clinoptilolite, as part of the basic research, the capacity of PMA-Zeolite with respect to environmental toxins (including the heavy metals lead, cadmium, arsenic, chromium, and nickel as well as the metabolic end product ammonia) was analysed *in vitro* using a

gastrointestinal model. In this case, the ion exchange capability, and the resultant selective binding of defined pathogenic substances, was clearly proven. Details on the structure and mechanism of action of PMA-Zeolite can be found in the background information section.

#### **Operative hypotheses and proof of efficacy:**

The defined main mechanism of action plays a fundamental role in demonstrating the mode of action of PMA-Zeolite at the site as well as validating various operative hypotheses based on this defined mechanism of action. The data, insights, and trends from preclinical studies (*in vitro* and *in vivo*) – especially clinical gold standard studies – form the basis for further validation (human applications).

#### **Evidence-based proof of the intended main effect:**

One hypothesis based on the main mechanism of action (selective binding of pollutants *in vitro* gastrointestinal model) is the strengthening of the functionality of the intestinal wall barrier. This promising hypothesis was proven in a randomised placebo-controlled clinical gold standard study in which a significant decrease in the bio-marker zonulin (and thus an improvement/strengthening of intestinal wall function/integrity) was achieved. This represents the main intended action of PMA-Zeolite.

*Undigested food particles, toxins, and bacteria*

**ZONULIN**

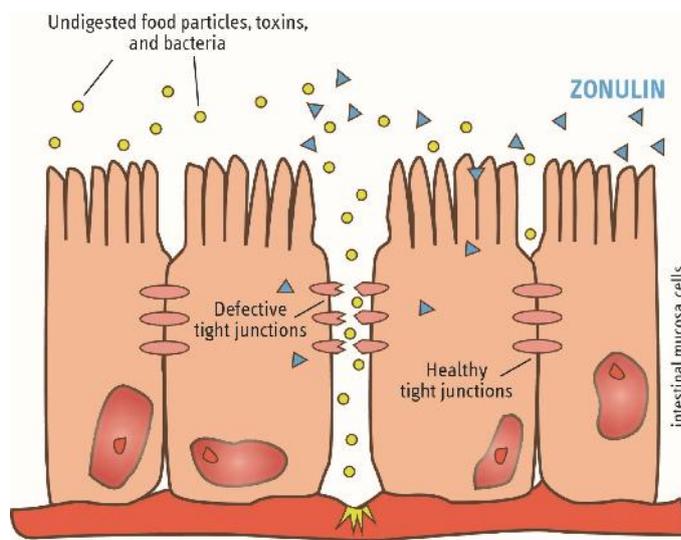
*Defective tight junctions*

*Healthy tight junctions*

*Intestinal mucosa cells*

*Tight junctions = tight connection*

*Zonulin = a protein that the tight junctions open and close when necessary. Too much zonulin means more permeability.*



**Tight junctions** = tight connection

**ZONULIN** = a protein that the tight junctions open and close when necessary. Too much zonulin means more permeability.

**Figure 4:** Representation of the bio-marker zonulin, which is correlated with a permeable intestinal wall barrier (defective tight junctions).

### **Validation of secondary effects:**

The **secondary effects** resulting from the main mechanism of action were confirmed by additional fundamental and application studies. This involves the validation of the products based on the intended main physical mechanism of action e.g. relief of the gastrointestinal tract and ultimately the detoxification organs, especially the liver.

With respect to the secondary effects, *in vivo* experiments were performed in a model organism in order to study the regenerative ability of liver cells following the administration of PMA-Zeolite. Likewise, anti-oxidative secondary effects, which are closely connected with the principal mode of action, were further investigated and described. Based on this, preclinical data obtained with PMA-Zeolite was validated by healthcare professionals or experts.

The following study summaries on the strengthening of the intestinal wall barrier, the support of detoxification, and the indirect systemic effects (secondary effects) are intended to provide insight into the long-term research activities with the natural mineral PMA-Zeolite. Any redundancies in the individual observations are intended and should contribute to a better understanding of the individual section, especially if it is not read in the context of the entire document.

## **Study summaries**

### **Safety/toxicology**

#### **Physical and chemical characterisation of materials**

The physical and chemical features of the PMA-Zeolite are essentially characterised through its composition (physical/chemical/mineralogical) as well as the selectivity series and particle nature.

The most important physical characteristics are the stability towards acids and bases (pH 1.2–11) as well as the high temperature stability (up to 450°C). The stability is thus indicated in terms of the physiological conditions in the gastrointestinal tract (the site of action of PMA-Zeolite). An important quality characteristic in terms of the chemical composition is a clinoptilolite fraction > 80% and a correspondingly high silicon to aluminium ratio (> 5:1). Other quality parameters for the PMA-Zeolite include the clearly defined selectivity series, which indicates which contaminants (cations) are readily taken up and replaced with physiological cations (e.g. Mg<sup>2+</sup>, Ca<sup>2+</sup>, K<sup>+</sup>, and Na<sup>+</sup>). More detailed information on the characterisation and the physical mode of action of PMA-Zeolite can be found in the background information section.

Based on the fulfilment of the quality criteria, studies are required in order to demonstrate and document the safety for human applications. All safety related studies have been conducted with PMA-Zeolite produced or processed by Panaceo.

#### **Toxicological investigations**

The basis for evaluating the bio-compatibility of this Class IIa medical product is DIN EN ISO 10993. The following basic tests were carried out with the PMA-Zeolite processed by Panaceo.

##### ➤ **Cytotoxicity**

The cytotoxicity tests revealed that the sample extracts did not lead to critical biological damage of the test cells and can thus be classified as non-cytotoxic.

##### ➤ **Sensitisation and irritation**

The irritation and sensitisation tests revealed that the products do not cause toxic or allergic reactions. In addition to the required investigations, the following tests were conducted by Panaceo in order to ensure additional safety.

##### ➤ **Toxicity (acute/sub-acute/chronic)**

##### ➤ **Genotoxicity**

##### ➤ **Reproductive and developmental toxicity**

These toxicity studies were performed by Dr Pavelić in accordance with the OECD guidelines. Dr Pavelić concluded that PMA-Zeolite did not have any toxic or mutagenic effects in acute, chronic, or sub-chronic toxicity studies.

### **Summary of the findings:**

After evaluating the investigations and tests (physical and chemical characterisation of materials as well as toxicological studies) in which the *in vitro* and *in vivo* results confirmed each other, **the active agent PMA-Zeolite as well as the medical products developed from this can be classified as safe for human application.**

## The main mechanism

### The detoxifying potential of PMA-Zeolite<sup>23, 24</sup>:

The *in vitro* studies performed in July 2014 at the University of Rijeka under the direction of Dr Krešimir Pavelić demonstrate that zeolites can absorb environmental contaminants such as organochlorine pesticides and heavy metals. They can thus make a substantial contribution to the detoxification of the human body.

Although many persistent organochlorine compounds have been banned in Europe, certain environmental toxins prone to bio-accumulation (e.g. Aldrin) are still present in the soil or surface water and can thus enter the food chain.<sup>25</sup> Heavy metals (e.g. cadmium or lead), which are widespread air pollutants, accumulate in the soil and subsequently the food chain.<sup>26</sup> They can therefore account for more than 20 times the legally permissible value in our food and thus exceed the toxicological reference values for daily intake.<sup>27</sup>

Because they are prone to bio-accumulation, they can also slowly accumulate in the body and lead to negative health consequences. For example, studies have indicated a relationship between exposure to the pesticide  $\beta$ -HCH and the development of neurological diseases or the induction of oxidative stress.<sup>28</sup> In addition, there is no placental barrier that counteracts the passage of organochlorine compounds between mother and child. Among other things, chronic exposure to heavy metals can lead to liver and kidney damage.<sup>29</sup>

In a two-part *in vitro* study in an artificial gastrointestinal model, it was investigated whether PMA-Zeolite can support detoxification. Under the *in vivo* conditions of the gastrointestinal environment, PMA-Zeolite selectively absorbed pathogens from food loaded with multi-toxins (as they occur in everyday life). To simulate the natural gastric and intestinal environment (pH adjusted), test solutions were prepared, consecutively added to the pesticides to be tested, extracted, and subjected to chromatographic analysis. It was shown that PMA-Zeolite absorbs a series of organochlorine compounds (pesticides).

In another series of experiments, the uptake capacity of zeolite with respect to heavy metals was investigated. Using various doses of PMA-Zeolite and a spectrometric method, the optimal binding of lead, cadmium, arsenic, chromium, and nickel was demonstrated.

Pestizid	Absorbiert durch PMA-Zeolith
$\beta$ -HCH	✓
Trans-chlordane	✓
Aldrin	✓
4,4'-DDD	✓
4,4'-DDE	✓

**Table 2:** Overview of organic chlorogenic compounds that are absorbed by PMA-Zeolite

### Summary of the findings:

In an artificial gastrointestinal model, it was demonstrated that PMA-Zeolite binds heavy metals such as lead, cadmium, arsenic, chromium, and nickel as well as the residues of pesticides such as organic chlorogenic compounds originating from foodstuffs according to the physical mechanism of action. **The overall stress on the gastrointestinal tract is reduced, thereby proving the selective binding or detoxification potential of PMA-Zeolite.**

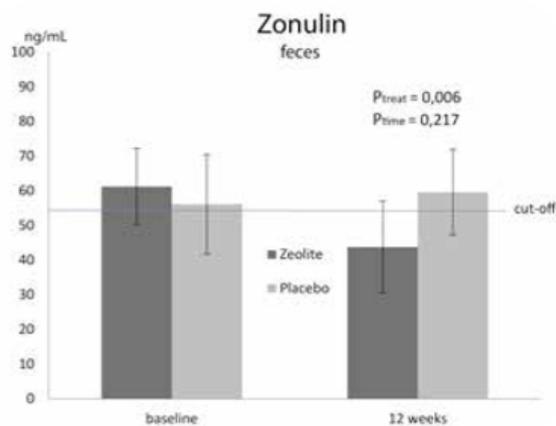
## Dr Krešimir Pavelić

“In our research, we have seen that zeolite-clinoptilolite has outstanding properties and opens up new possibilities in the fields of biology and medicine”.

### Intended main action – strengthening the intestinal wall barrier Gold-standard study

Under the guidance of Dr Manfred Lamprecht, a placebo-controlled randomised double-blind study was conducted at the Green Beat Institute for Nutrient Research and Sports Nutrition and the Institute of Physiological Chemistry at the Medical University in Graz from December 2012 to July 2014. In reference to the intestinal wall as a vital protective barrier of the body, for the purposes of this clinical gold standard study, all subjects were monitored in terms of stress-induced leaky gut syndrome. It is well known that various physical stresses can lead to a disturbance of intestinal wall function (leaky gut syndrome). A subject group of endurance-trained individuals was used. The effects of PMA-Zeolite on intestinal wall permeability and the integrity of the tight junctions were examined using the enterotoxin zonulin (informative bio-marker for intestinal wall integrity/permeability). Likewise, other parameters such as anti-inflammatory cytokines, membrane proteins, and a mineral panel were evaluated.

The subjects were 52 healthy, endurance-trained men and women aged 20–50 years. After a wash-out phase to remove all dietary supplements and sports nutrition products, they were given either a PMA-Zeolite supplement (2g/day) or a placebo for 12 weeks. Stool and blood tests were taken at 0 and 12 weeks in order to determine the defined bio-markers and parameters.



**Figure 5:** Zonulin concentration in the stool of the treatment or placebo group at 0 and 12 weeks of supplementation. The values represent means  $\pm$  SD,  $P < 0.05$  (ANOVA),  $n = 27$  (treatment),  $n = 25$  (placebo)

### Explanation of ZONULIN:

The regulator protein zonulin is a suitable marker for measuring the permeability of the intestinal mucosa or intestinal wall. Zonulin regulates the exchange of liquid, macromolecules, and leukocytes between the bloodstream and the intestinal lumen. It also protects the sub-epithelial layers. Different stimuli cause the intestinal epithelial cells to release zonulin into the gut lumen and blood vessels. Examples are the direct contact with bacteria in the case of a lacking or intermittent intestinal mucus layer and contact with gliadin.

Parameter/ bio-markers	Result	Interpretation
Zonulin	significant change (decreased) ( $p < 0.05$ )	Both groups initially showed consistently high zonulin levels ( $> 30$ ng/ml, which is well above the norm) in the stool. This is indicative of a disturbed intestinal wall permeability. After supplementation for 12 weeks, there was a significant reduction in the zonulin levels ( $p < 0.05$ ) of the treatment compared with the control group in which there were almost no changes.
IL-10 (Interleukin 10)	Trend ( $p < 0.1$ )	After supplementation for 12 weeks, there was a slight increase in IL-10, an immuno-modulator in the intestinal tract. This means that an anti-inflammatory tendency was observed.
Other parameters (e.g. mineral levels)	No significant change	At the beginning and end of supplementation, there were no significant differences between the treatment and placebo groups.

**Table 3:** Summarised results of the Lamprecht Gold Standard Study

The zonulin docks to the receptors on the surface of intestinal epithelial cells and triggers a signalling cascade through which the cytoskeleton of the cell shrinks. As a result, the tight junctions open. If the zonulin-mediated opening of the tight junctions repeated and reinforced, a leaky gut syndrome develops.<sup>31</sup>

The results summarised in Table 3 indicate that the group under examination (professional athletes who had suffered from a stress-induced intestinal barrier dysfunction and were thus handicapped) experienced a rapid normalisation and resumption of intestinal function following supplementation with PMA-Zeolite. The slight increases in IL-10, which was documented as a secondary effect supported/relieved the immune system. This means that the administration of PMA-Zeolite showed a secondary anti-inflammatory effect on the intestinal wall. The study thus shows that there is a significant decrease in the bio-marker zonulin following supplementation with PMA-Zeolite. This means that the intestinal wall was relieved or the intestinal wall integrity was strengthened. A relief of the intestinal wall can thus help alleviate leaky gut syndrome and thereby the associated chronic inflammation and secondary diseases.

In connection with leaky gut syndrome, it should be noted that confounding medical conditions, including irritable bowel syndrome, are associated with these symptoms. Dr Norbert Schulz made application observations with respect to irritable bowel symptoms and noted that PMA-Zeolite successfully relieved symptoms in patients who had undergone stationary regeneration treatments.<sup>32</sup>

### Summary of the findings:

In this placebo-controlled randomised double-blind study (Dr Lamprecht, 2015, Green Beat Institute, Graz, Austria) on the strengthening of the intestinal wall barrier, a 12-week intervention of physically stressed (endurance trained) **subjects with PMA-Zeolite resulted in improved intestinal wall**

**function/integrity as well as an anti-inflammatory tendency. The immune system can be supported and an endotoxemia can be prevented.** Because athletes who exercise excessively are often confronted with intestinal problems and have high zonulin values, they can benefit from nutritional intervention as well as those who are exposed to chronic physical stress stimuli.

### **Validation of secondary effects**

Secondary effects are based on hypotheses grounded on the main physical mechanism of action (excretion of defined pathogenic substances via the gastrointestinal tract according a clearly defined key-lock-principle) as well as the intended main effect (strengthening/support of intestinal wall integrity).

The body is a holistic system. Each and every cell is therefore important for proper function and good health. Because the various bodily functions overlap, an overloading of system components can negatively affect the entire body. Conversely, the relief of specific parts of the system (e.g. the gastrointestinal tract) can positively affect the body. The gastrointestinal tract is often the origin of various diseases. An increased intestinal wall permeability is often associated with irritable bowel syndrome as well as enhanced immune reactions (allergies and autoimmune reactions) or an overload of the liver function.

If the causes of diseases are eliminated at the source, unwanted circulations (in terms of far-reaching consequences) can be affected or even interrupted or prevented. In this sense, according to its main physical mechanism of action, PMA-Zeolite can bind contaminants in the gastrointestinal environment<sup>33</sup>, strengthen the intestinal wall function and/or the intestinal wall barrier function<sup>34</sup>, and bring relief to the remaining body systems. Indirect systemic side-effects (i.e. secondary effects) are described in the following studies.

### **Basic research**

Investigation of the antioxidant activity of Panaceo<sup>35</sup>

Dr Peter M. Abuja investigated the anti-oxidant activity of Panaceo at the Medical University of Graz. The aim was to document the antioxidant activity and the mechanism of action of PMA-Zeolite.

A certain amount of free radicals are generated in the human body. Increasing levels of environmental contaminants lead to an excess of free radicals (ROS), which cannot be processed by the body. The increased release of ROS can be attributed to environmental contaminants (e.g. air pollutants, heavy metals, and pesticides), a high-fat diet, stimulants (e.g. tobacco and alcohol) and the metabolism of various pharmaceuticals. One test entailed measuring the property as a direct antioxidant as well as investigating various emulsion oxidation approaches simulating the biologically important lipid peroxidation processes and thus the effect on the formation of free radicals.

In summary, thanks to its ion exchange capability, PMA zeolite-clinoptilolite is even effective at physiologically high ionic strengths and low pH values. As a primary, non-enzymatic antioxidant, it hinders the catalytic formation of radicals through transition metal ions – *in vitro* in both pure lipid emulsions and more complex systems. Cells can therefore be protected from free radical (ROS) induced cell death.

It has been proven that using PMA zeolite results in decreased formation of free radicals. This is not due to a chemical reaction with the radical but is rather based on a physical mechanism – namely the uptake (and thus reduction) of catalysts that trigger oxidative-stress (e.g. heavy and transition metals in the gastrointestinal tract). Through its micro-porous structure and cation binding capacity, the natural mineral reduces oxidative damage through free radicals in a physical manner (e.g. reduction of lipid peroxidation) by reducing catalysts that trigger oxidative stress. The reduced formation of free radicals thus represents an indirect physical reduction (as opposed to direct chemical reaction with vitamin C or E in the blood). This can be regarded as systemic secondary effect of the main mechanism of action.

### **Summary of the findings:**

In this pre-clinical study (Dr Peter Abuja, 2006, Institute of Biophysics and X-Ray Structure Research, Graz, Austria), which investigated the anti-oxidative effect of Panaceo, it was shown **in both lipid emulsions as well as more complex systems that PMA-Zeolite (as a primary, non-enzymatic**

**antioxidant) reduces the catalytic formation of radicals by binding transition metal ions. The formation of free radicals (ROS) can this be reduced by up to 50%.**

Alzheimer's animal model – reduction of oxidative damage<sup>36</sup>

Here, the antioxidant and protective properties of PMA zeolite clinoptilolite (more precisely: protection against oxidative damage in neurodegenerative diseases) were examined. This study is also related to the overloading of the body by environmental catalysts and the issue of the protective effect of PMA-Zeolite on the anti-oxidative system (more precisely: neuronal cells).

After pro-oxidative stimulus, **(i) *in vitro*** cell death and oxidative stress were determined in a neuronal-like cell line. The antioxidant activity and amyloidogenic processing of amyloid beta were **(ii) *in vivo*** evaluated in animal models (mice) after five months of enriching the drinking water with PMA zeolite-clinoptilolite

The experimental designs used in neural cells (*in vitro*) and model organisms (*in vivo*) clearly show the positive effect of activated zeolite-clinoptilolite (PMA-Zeolite) in neurodegenerative diseases such as Alzheimer's. Mitochondrial production of reactive oxygen species (ROS), which have a key role in the regulation and control of the survival or death of the cell (by interacting with cellular macromolecules and signal transduction pathways) was achieved **(i) *in vitro*** following treatment with zeolite. **(ii) *in vivo*** through the activation of metallo-enzymes (SOD1 and SOD2; superoxide dismutase, endogenous antioxidant enzymes and effective free-radical scavengers). Moreover, a decrease in amyloid plaques (misfolded peptides, which are deposited between the neurons and tau fibrils, twisted protein fibres, inside of brain cells and are characteristic of Alzheimer's disease) was measured in the brain.

In particular, the gastrointestinal tract (defined active area of the PMA-Zeolite) is exposed to a series of relevant pathogenic substances (e.g. heavy metals and pesticides). Through its selective ion exchange capabilities, zeolite can counteract this overloading. Heavy metal ions or transition metal ions are thus exchanged with the free cations incorporated in the zeolite (i.e. Na<sup>+</sup>, K<sup>+</sup>, Ca<sup>2+</sup>, and Mg<sup>2+</sup>). The results of the study, in particular the increase in the endogenous antioxidant enzyme superoxide dismutase (SOD), which is an effective free radical scavenger, can be attributed to the release of minerals (manganese or copper and zinc) by the PMA-Zeolite. The aforementioned minerals are cofactors in the activation of metallo-enzymes such as SOD1 and SOD2. These can protect the body against oxidative damage.

In the course of this study, PMA-Zeolite afforded significantly better results than conventional natural zeolite-clinoptilolite.

#### **Summary of the findings:**

In this pre-clinical study (Dr Memo, 2013, University of Brescia, Italy), the protective effect of PMA-Zeolite against oxidative damage in neurodegenerative diseases was observed under both *in vitro* and *in vivo* conditions. The mitochondrial production of **reactive oxygen species (ROS), which play a key role in the regulation and control of the survival or death of the cell was reduced *in vitro* by treatment with PMA zeolite.** *In vivo*, it was found that PMA-Zeolite contributes to the increase in the endogenous antioxidant metallo-enzymes SOD1 and SOD2 (effective free radical scavengers and formed as co-factors with the help of trace elements) through the release of trace elements. Moreover a significant reduction of amyloid plaques and total amyloid levels was observed in mice treated with PMA-zeolite compared to the control group. **Through the release of selective minerals and trace elements, PMA-Zeolite can support antioxidant processes.**

#### **Study on partial hepatectomy - supporting the regenerative capacity of the liver<sup>37</sup>**

University of Rijeka, carried out under the direction of Dr K. Pavelić. In a model organism subjected to partial hepatectomy (70%), it was investigated whether the regenerative capacity of the liver cells can be supported by supplementation with PMA-Zeolite. In our culture, stresses (including environmental contaminants) steadily increased, thereby increasing free radicals (ROS), which can no longer be

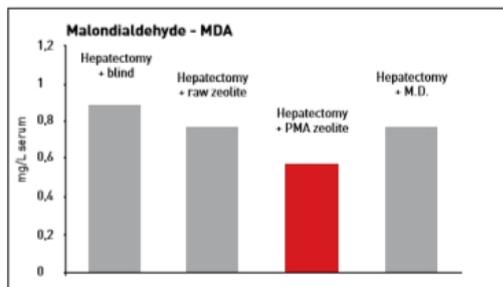
processed by our bodies. This detoxification capacity of our bodies is thus overloaded, and individual organs – particularly the liver – are exposed to increasing levels of oxidative stress.

In a complex model organism, the substances to be supplemented (PMA-Zeolite, untreated zeolite-clinoptilolite, and M.D.) were administered one week prior to surgery in which 70% of the liver mass was removed. The liver tissue and blood serum were analysed after supplementation and following the 70% hepatectomy.

In addition to a general significantly better effect of PMA-Zeolite on liver regeneration compared with the untreated zeolite-clinoptilolite and M.D., the most significant result of this study was the increase in the antioxidant capacity of the liver cells. A reduction of malondialdehyde (MDA) level and an increase in reduced glutathione (GSH) levels were observed.

#### Detailed results for MDA:

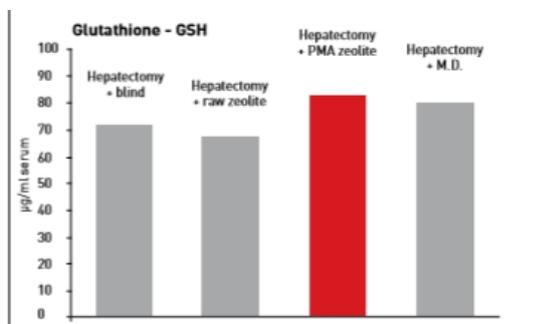
After supplementation with PMA-Zeolite, the levels of this important bio-marker for oxidative stress were significantly reduced. This indicates the immediate reduction of oxidative stress. After supplementation with PMA-Zeolite, the MDA plasma levels were significantly lower than for M.D. The same was observed in a comparison with untreated zeolite-clinoptilolite. The PMA-Zeolite thus afforded a significantly better effect than both untreated zeolite and M.D., an agent often used as a liver therapeutic.



**Figure 6:** Malondialdehyde (MDA) levels in the model organism after partial hepatectomy (70%) ± SD (mg/l serum). Four groups were compared: 1. Hepatectomy without further treatment (blind) 2. Hepatectomy and supplementation with raw zeolite; 3. Hepatectomy and supplementation with PMA zeolite; 4. Hepatectomy and supplementation with liver therapeutic agent.

#### Detailed results for GSH:

Treatment with PMA-Zeolite increased plasma levels of GSH, one of the main endogenous antioxidants. Treatment with PMA-Zeolite led to higher values than for M.D. and untreated zeolite-clinoptilolite. GSH plays a key role in protecting the cells against reactive oxygen species (ROS), xenobiotics, and heavy metals.<sup>38</sup> The regulation of GSH is thus seen as an important factor with respect to the progression of liver diseases. Too little GSH in the liver could lead to hepatocellular cell death.



**Figure 7:** Glutathione (GSH) levels in the model organism after partial hepatectomy (70%) ± SD (µg/ml serum). Four groups were compared: 1. Hepatectomy without further treatment (blind) 2. Hepatectomy and supplementation with raw zeolite; 3. Hepatectomy and supplementation with PMA zeolite; 4. Hepatectomy and supplementation with liver therapeutic agent

As demonstrated in this study, thanks to its micro-porous structure and cation binding capacity based on the main physical mechanism of action in the gastrointestinal tract, PMA-Zeolite not only protects endogenous anti-oxidants (GSH) but also reduces oxidative damage caused by free radicals (e.g. reduction of lipid peroxidation).

As a primary, non-enzymatic antioxidant, it hinders the catalytic formation of radicals through transition metal ions – *in vitro* in both pure lipid emulsions and more complex systems – in order to protect cells from a free radical (ROS) induced cell death.<sup>39</sup> This binding of transition metals can explain the anti-oxidative effect and consequently the decrease in malondialdehyde levels. In both neuronal cells (in vitro) and the model organism (in vivo), it was found that through the release of trace elements, PMA-Zeolite can activate metallo-enzymes (SOD1 and SOD2; superoxide dismutases) and thus protect against oxidative damage.<sup>40</sup>

The results described can be attributed to the main physical mechanism of action. The absorption capacity for defined heavy metals (see *in vitro* study in gastrointestinal model of Dr Pavelić) and cadmium in particular as well as the release of selective minerals and trace elements and the resulting activation of superoxide dismutase support the hypothesis that as a secondary effect, PMA-Zeolite can influence the alleviation of oxidative stress in the case of liver problems. Contaminants such as cadmium are taken up by PMA-Zeolite and must therefore not be bound by GSH. There are thus higher amounts of GSH available to actively protect the cell.

#### **Summary of the findings:**

In the *vivo* study in the model organism, which investigated the support of the regenerative capacity of the liver following partial hepatectomy, it was shown that **supplementation with PMA-Zeolite alleviated oxidative stress in the case of liver problems**. As an indirect systemic secondary effect, which can be traced to the main physical mechanisms of action of PMA-Zeolite in the gastrointestinal tract, **the regenerative capacity of the liver cells following partial hepatectomy (70%) was supported**. The most telling result here is an increase in the antioxidant capacity as demonstrated by the **reduction of malondialdehyde (MDH) and the increase of reduced glutathione (GSH)**. Moreover, PMA-Zeolite proved to be more effective than untreated zeolite products and active substances.

#### **Human studies – validation**

##### **Influence on the oxidative system of clinically healthy subjects<sup>41</sup>**

The present study serves to confirm the anti-oxidative effect of PMA-Zeolite in humans through the measurement of free radicals.

In 22 subjects (an equal number of men and woman), the influence of daily supplementation of 6 g PMA-Zeolite (divided into three doses) on the oxidative system was investigated. The duration of application was approx. one month.

To determine the oxidative state, a blood investigation was performed with FRAS (free radical analytical system) and the d-ROMS test (ROM = reactive oxygen metabolites, markers and amplifiers of oxidative stress). The investigations of oxidative stress were conducted using a pre-post comparison. In other words, the blood was tested before and after the application of PMA-Zeolite.

In summary, it can be assessed that approx. one month of supplementation with PMA-Zeolite can considerably reduce excess levels of free radicals. Surprising were the findings from hormone-treated women, who exhibited high-levels of oxidative stress, which pose a high risk for chronic diseases. This pre-supplementation data of the investigation shows that it could be useful to implement the d-ROMS test into routine diagnosis in practical and clinical medicine in order to prevent oxidative stress.

#### **Summary of the findings:**

This application observation in humans (Dr Thoma, Villach, 2006, Private Clinic, Austria) **indicates that a one month supplementation with PMA-Zeolite can considerably reduce the levels of free radicals in clinically healthy subjects**.

In conjunction with the positive influences on the endogenous anti-oxidative system from this observation and basic research, Dr Bachl and Dr Knapitsch performed a randomised, placebo-controlled double-blind study in humans.<sup>42,43</sup> A slower increase in lactate concentration was measured in the blood. This can be traced to the effect of PMA-Zeolite as an enzyme promoter. Through the release of trace elements (as co-factors), there is a connection to carbonic anhydrase. This, in turn, has a direct influence on CO<sub>2</sub> metabolism. A connection can thus be made to lactate reduction and its effect on the body's antioxidant system.

The basis of this secondary effect (anti-oxidative effect of PMA-Zeolite) forms the main mechanisms of action of zeolite-clinoptilolite i.e. the reduction of pathogens in the gastrointestinal environment. This also includes the physical reduction of transition metal ions, which contribute to the formation of free radicals. Thanks to the trace elements (co-factors) supplied through ion exchange, endogenous anti-oxidative enzymes can be supported. This leads to a reduction in free radicals.

As a result, the muscle is left with more oxygen, thereby initiating a shift from aerobic to anaerobic performance (i.e. reduction of lactate levels at the same load). This secondary effect leads to a relief of the body; energy that would otherwise be required to degrade harmful substances and repair cells is released.

### **Austria-wide pilot study – natural and measurable influence on the reduction of elevated liver parameters<sup>44</sup>**

In the autumn of 2013, an Austria-wide pilot study was started in order to investigate a positive support or relief of the endogenous detoxification system by PMA-Zeolite. It was intended to document the positive effect of PMA-Zeolite on liver metabolism in subjects with increased liver values with various unspecified causes. The evaluation was based on the blood parameter alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (γ-GT), which indicates a functioning detoxification.

An evaluation of over 130 cases sent in by approx. 100 participating doctors revealed a significant reduction of the aforementioned enzyme activities in more than two thirds of all subjects after 1–3 months of supplementation with PMA-Zeolite. The reduced enzyme activity indicates that increased liver parameters can be naturally reduced without further pharmacological stress.

This result is surprising because neither the inclusion nor exclusion criteria were defined nor was compliance checked. The reduction of increased liver parameters brought on by the intake of PMA-Zeolite also means that the detoxification systems can be relieved and the functional or regenerative capacity of other organs can be supported through the main physical mechanism of action and the main intended action in the gastrointestinal tract.

The data on the positive influence of PMA-Zeolite on liver parameters suggest that through its ion exchange capacity, PMA-Zeolite binds harmful substances from the environment, our diets, and our metabolism in the gastrointestinal tract and naturally discharges them via the stool. This can be traced to the main physical mechanism of action. Through the detoxification of the gastrointestinal tract, the detoxification organs, especially the liver, which is a metabolic hub, are relieved.

In this context, the close association between liver and medication intake should be mentioned. Many years ago, viruses were still considered to be the main cause of acute liver failure. However, today, one half of all cases can be attributed to medications.<sup>45</sup> The reduction of any additional stress for the gastrointestinal tract and liver resulting from the intake of PMA-Zeolite can be applied as a possible adjuvant in drug therapies.

### **Summary of the findings:**

This Austria-wide pilot study (Dr Triebnig/Panaceo, 2014, Austria) on the influence of PMA-Zeolite on the reduction of increased liver parameters showed **the tendency towards reducing liver values in the case of enhanced blood parameters following 1–3 months of supplementation with PMA-Zeolite**

This positive effect on liver metabolism is based on the intended main effect as well as the main mechanism of action of PMA-Zeolite in the gastrointestinal tract and **occurs without additional pharmacological stress** in subjects with increased liver parameters of various unspecified origin.

### Study – improvement of liver and kidney parameters through PMA-Zeolite in the case of eating disorders <sup>46</sup>

The application observation with a parallel group design on the effect of PMA-Zeolite on the improvement of the uptake of vital nutrients was conducted under the direction of clinical psychologists Dr Dieter Weber and Dr Gustav Raimann at the Paracelsus Sanatorium in Villach in 2012. The in-patient treatment of different forms of eating disorders (anorexia nervosa and bulimia nervosa) formed the framework. Blood parameters and the BMI (body mass index) were recorded in order to determine whether there is an influence.

Using an identical treatment method and in compliance with a strict therapy plan, a treatment group (11 individuals) was given one level measuring spoon (approx. 3 g) of PMA-zeolite three times daily at mealtimes with water. The control group (10 individuals) took their meals without supplementation. During the treatment, various blood parameters (for immune system, liver, kidneys, digestive, and fat metabolism) as well as body measurements and defecation were logged.

The study results, which were blindly evaluated, shows that the BMI of the treatment group improved by 30% more than the reference group. This difference was significant. In the treatment group, there was also a substantial improvement in liver enzymes (GPT, GOT, and  $\gamma$ -GT) as well as a decrease in creatinine levels. Creatinine is excreted in the urine. Elevated values can indicate a kidney deficiency. In the treatment group, there was also a significant reduction in cholesterol values.

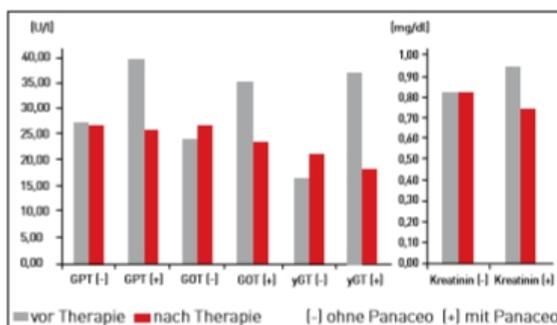
#### Summary Statement of the parameters measured (see illustration on page 18):

**GPT (Glutamate pyruvate transaminase)**, currently known as ALT (alanine aminotransferase): There was an approx. 50% decrease in GPT levels following treatment. This indicates a return to the optimal range. The GPT values of the control group remained constant.

**GOT (Glutamate oxaloacetate transaminase)**, currently known as AST (aspartate aminotransferase): In the treatment group, elevated values decreased and normalised during treatment. In contrast, in the control group, a slight elevation was observed.

**$\gamma$ -GT (gamma-glutamyl transferase)**: Before treatment, the  $\gamma$ -GT values of the treatment group were in the upper limit range. Following treatment, the parameter decreased by 50%. Conversely, the values slightly increased in the control group.

**Creatinine**: Following supplementation with PMA zeolite, there was a considerable decrease in the level of creatinine in the treatment group. During treatment, the creatinine concentrations in the control group remained constant.



**Figure 8:** Summary of the liver and kidney values. The data showed that treatment with zeolite induced a significant reduction in the markers.

Through the results, a relationship can be re-established between the intended main effect and the main mechanism of action of PMA-Zeolite. Because the PMA-Zeolite can take up defined and potentially

dangerous materials in the gastrointestinal tract through its selective filter effect, a cleansing or detoxification takes place.

Furthermore, through ionic exchange, trace elements and minerals were selectively supplied. Through the uptake of potentially dangerous materials<sup>47</sup> as well as the effect of PMA zeolite as an antioxidant<sup>48</sup>, the digestive organs are relieved, and possible repair and anti-inflammatory mechanisms of the intestinal wall are activated. This cleansing of the gastrointestinal tract can be explained by the potential improvement in nutrient uptake. This can be explained by the significant increase in BMI in the Panaceo group in the present study. Through the detoxifying or cleansing effect of the PMA zeolite in the gastrointestinal tract and the strengthening of the intestinal barrier function, the liver, which is also an important detoxification organ, is also relieved. The data collected blindly in this clinical application study are consistent with the findings of the pre-clinical study on liver regeneration capacity.<sup>49</sup>

Thanks to the anti-inflammatory effect on the intestinal wall, vital nutrients can be better processed. Through the relief of the liver and the liberated capacities for the further processing of nutrients (carbohydrates, proteins, and fats), the improvement of the cholesterol values as an indirect systemic secondary effect can be explained. The influence of PMA-Zeolite on the reduction of cholesterol was also documented in pre-clinical studies.<sup>50</sup> The considerably improved regeneration of the liver and kidney parameters in the treatment group compared with the reference group can be traced back to the direct relief effect of PMA-Zeolite as well as the simultaneous release of essential minerals and trace elements, whereby an additional support of the self-regulation (enzyme promoter) can be explained.

#### **Summary of the findings:**

The study results on the improvement of liver and kidney parameters through PMA-Zeolite (Dr Weber and Dr Raimann, 2012, Paracelsus Sanatorium in Villach) showed a significant improvement of the BMI as well as a distinct normalisation of the liver and kidney parameters (GPT, GOT,  $\gamma$ -GT, and creatinine). It was thus shown that **PMA-Zeolite when administered can lead to a more rapid normalisation and resumption of intestinal function and that there is also a systemic connection with respect to improvement of nutrient uptake and the relief of the liver** through the defined main physical mechanism of action and the intended main effect in the gastrointestinal tract.

#### **Final consideration**

The studies described show that there is adequate data on the PMA-Zeolite produced by Panaceo. Its safety, its main intended action, and the main physical mechanism of action in the gastrointestinal tract as well as a series of indirect systemic secondary effects on the detoxification system as well as the entire body have been demonstrated through pre-clinical, clinical, placebo-controlled, and double-blind studies (including gold standard).

The excellent results and interim results form a solid basis for future studies focussing on further exploration of the potential contaminant absorption behaviour, the effects on the microbiome and intestinal wall functionality, and the related systemic secondary effects on the body.

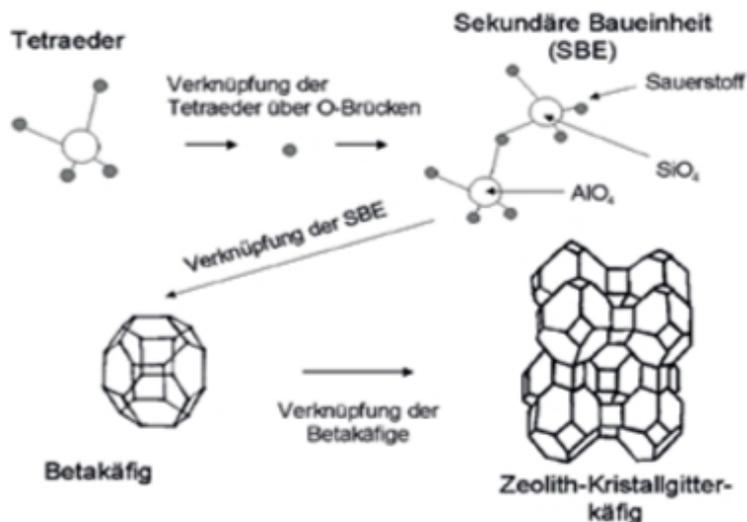
In summary, it should be noted that the research activities of Panaceo, which are based on the latest findings from the PMA-Zeolite research are conducted in accordance with the highest scientific quality standards.

**The conception and implementation of our R&D activities involve being able to guarantee safe and effective products that are able to afford relief from increasing negative environmental influences by reducing exposure to contaminants and strengthening the intestinal barrier function.**

#### **Background information on PMA-Zeolite**

As mentioned at the beginning of this leaflet, there are over 200 natural and artificial zeolites. The specific natural zeolite-clinoptilolite used by Panaceo as a starting mineral for their certified medical products consists of a microporous framework structure made of alumina and silica tetrahedra. Aluminium and silicon atoms are interconnected by hydrogen atoms. This results in a stable structure

of uniform pores and/or channels which naturally contain water that can be removed through heating without changing the zeolite structure. This stability is demonstrated in both acidic and basic environment as well as at temperatures up to 450°C.



**Figure 9:** Structures of the zeolite crystal lattice made of  $\text{SiO}_4$  and  $\text{AlO}_4$ . The microporous volcanic mineral zeolite is traversed by fine crystal lattice tubules (with a diameter of approx. 0.4 nm).

Because this involves a naturally occurring mineral, the quality is decisive for the anticipated medical success. As is the case with any naturally occurring element, there are variations in the natural composition of zeolite clinoptilolite. These depend on the location of occurrence.

Panaceo therefore regularly checks the quality of the deposits and only purchases the starting material from companies that have been audited in advance. In addition to a clinoptilolite content of > 80%, one of the most important mineralogical quality parameters is a high Si to Al ratio (> 5:1). In addition, care is taken to ensure the nearest possible occurrence and a careful mining method in order to minimise transport and protect the environment. The result is the optimum raw material as a basis for further processing to PMA-Zeolite.

**The PMS process technology is a unique method in which the particles of the raw materials (zeolite-clinoptilolite) are accelerated at very high kinetic energies and crush each other. In addition to the desired homogeneous micronisation, the crystal lattice is modified, thereby leading to a strongly negative surface charge. The now spherical and extremely jagged particles have an optimised outer surface and a mean grain size of 3–5  $\mu\text{m}$ . A calculation of the surface of PMA zeolite by the Technical University of Vienna revealed that for a total penetration depth into the pores, 1 g of the active ingredient produced by Panaceo has an effective surface of approx. 4000  $\text{m}^2$ .<sup>52</sup>**

Numerous investigations<sup>53, 54, 55</sup> have shown that the Panaceo-Micro-Activation process can yield a considerably higher efficacy than the starting material. The efficacy can be defined by the particle size, the effective surface, and the cation exchange capacity.

Differences in the absorption behaviour primarily arise from the pH of the environment. PMA-Zeolite has the highest absorption capability in ranges that most closely approximate the human digestive environment.

In summary, the enlarged surface of the micronised zeolite PMA is an important quality parameter and is simultaneously responsible for the increased efficacy (improved absorption capability).

### The main mechanism of action of PMA-Zeolite

The main mechanism of action of the unique natural cation exchanger PMA-Zeolite, which is pre-loaded with minerals and trace elements, is based on absorbing contaminants according to a clearly defined lock and key principle via the gastrointestinal tract and releasing minerals and trace elements because of the osmotic concentration gradient. As a result, PMA-Zeolite is not metabolised but rather completely combined with bound contaminants and naturally excreted with the stool. As a result, this material can no longer damage the intestinal wall—the “guardian” of our immune system. In accordance with the intended purpose, detoxification is supported (binding of defined pathogens in the gastrointestinal tract) and the intestinal wall barrier is strengthened.

The cause-effect relationship is fundamental to understanding the mechanism of action of the selective cation exchanger PMA-Zeolite. The best way to explain this is by an analogy with a medical product that is similar in purpose i.e. the removal of unwanted substances. As is the case with haemodialysis, the cleansing/detoxification/delivery of desired products is done via the blood. This protects the body and its organs, thereby preventing secondary diseases. The same principle is also used for zeolite. In the case of haemodialysis, ion exchange takes place via osmosis. In the case of zeolite, ion exchange takes place between the zeolite crystal lattice (negatively charged) and the cations to be absorbed (positively charged) because of a defined electromagnetic or electrostatic interaction.

The ion exchange of cations occurs based on the given selectivity of the natural mineral zeolite-clinoptilolite<sup>56</sup>, which is defined by a specific absorption number of specific elements. The molecular sieve function of the natural zeolite clinoptilolite defines a molecular selection via the pore size of only approx. 0.4 nm of the cavity system. It is important to understand that natural zeolite-clinoptilolites have a negative framework charge, which is balanced by cations that occur in the channel system. The cations include minerals such as sodium, potassium, calcium, or magnesium as well as trace elements such as zinc, manganese, or silicon, which often occur in dissolved form and are thus relatively easy to access and exchange. Through the defined sorption series, defined contaminants are taken up via ion exchange. In exchange, physiologically important minerals and trace elements are released. The sorption series of the natural zeolite-clinoptilolite, which forms the starting material of the PMA-Zeolite, includes caesium > ammonia > lead (greatest affinity for caesium). In the gastrointestinal model, it was demonstrated that the heavy metals arsenic, cadmium, chromium, and nickel are bound by PMA-Zeolite in the gastrointestinal tract.

Based on the high specificity of the PMA-Zeolite, interactions with oral medications can be well assessed. As a result of the molecular size and the necessary charge (cations), interactions are very unlikely. To minimise the risk, Panaceo recommends consulting your doctor before taking PMA-Zeolite with other medications. Doctors that have worked with PMA-Zeolite for many years recommend taking other medications 1 h before PMA-Zeolite (because the medication is resorbed while the PMA-Zeolite remains in the gastrointestinal tract).

**By reducing relevant contaminants through the binding of PMA-Zeolite in the gastrointestinal tract, the intestine and consequently the detoxification system – especially the liver – can be relieved and thereby supported. Panaceo medical products thus contribute to the prevention or alleviation of diseases through a supportive concomitant therapy (adjuvant and/or downstream application).**

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