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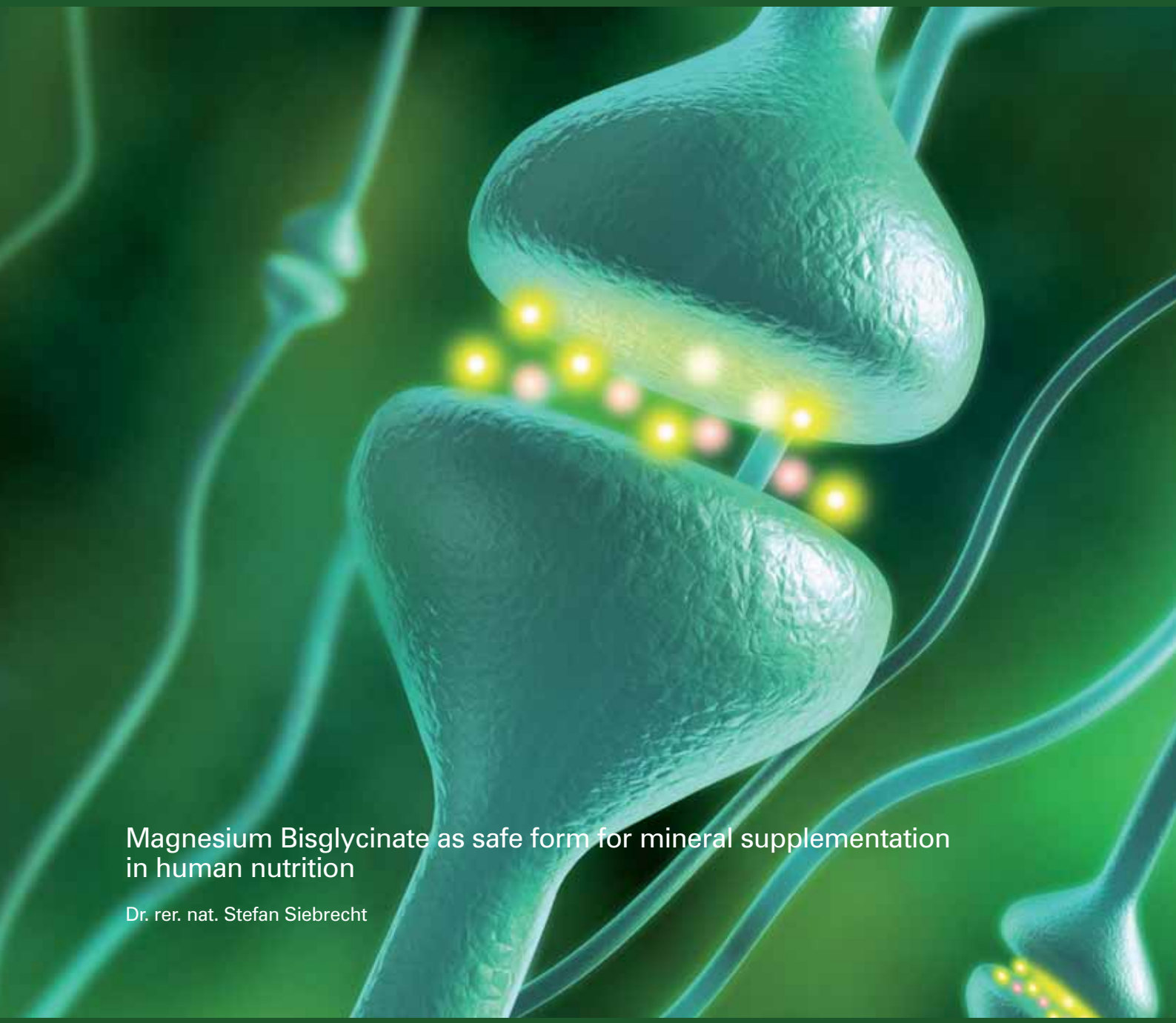

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Summary

Magnesium bisglycinate is a unique and safe form of magnesium that is useful for human nutrition. Magnesium bisglycinate is a stable and highly bioavailable chelate mineral complex that is absorbed in a different way via the dipeptide channel in the intestine and the magnesium bisglycinate does not compete with the ionic metals vying for the same transport sites in the small intestine. The chelate character reduces the competition with other minerals such as calcium for example and protects the magnesium from binding and precipitating dietary phosphates, Phytates, tannins, and roughage. Magnesium bisglycinate also does not suppress the absorption of other ionic elements being also required for nutrition and digestive irritation and toxicity is greatly reduced. Therefore magnesium bisglycinate is a very good tolerated and effective source for magnesium in human nutrition.

Introduction

Magnesium is one of the most important minerals in the body. Magnesium is the second most abundant intracellular cation and a cofactor for more than 300 metabolic reactions in the body *[Elin 1987, 1]*. Minerals play important roles as enzyme prosthetic groups and cofactors in anabolic and catabolic metabolism *[Underwood 1977, 2]*.

Mineral-Enzyme Interaction

- constitute part of the prosthetic group
- be an active part of the prosthetic group
- incorporation into the enzyme itself
- facilitating conversions by the enzyme
- inhibition of enzymatic activity
- play integral roles within the human enzymatic system

Magnesium distribution in the human body

Approximately 20 to 28 grams of magnesium occur in the adult human body. Of this total, 59% is in the bone, 1% is in the extracellular fluid and 40% resides in the muscles and soft tissues *[NRC, 1989]*. Part of the magnesium stored in the bones is in equilibrium with the serum, while the majority is more stable and stays in the bones. After bone, the muscle contains the highest amounts of magnesium which makes up to 25-40% of the total body's magnesium. Again here a part of the muscle magnesium is also in equilibrium with the plasma. Extracellular magnesium accounts for only 1% of total body magnesium.

The main regulation of body magnesium content in the plasma is via control of kidney magnesium reabsorption. This process is responsible to serum magnesium levels, which is responsive to magnesium intake. However kidney reabsorption of magnesium can also be influenced by other factors such as certain drugs and hormonal changes. In fact many situations that cause severe magnesium deficiency involve excess renal loss of magnesium.

The average plasma concentration is about 0.85 mM, with a range of 0.65 to 1.0 mM and appears to be regulated under tight control by the kidneys. More than 300 enzymes are known to be activated by magnesium and are included in such basic processes as glycolysis, oxidative respiration, active membrane transport, formation of cyclic-AMP and transmission of the genetic code. Magnesium is excreted through the feces and urine, although very efficient reabsorption mechanisms occur. In the serum, over half the magnesium is ionized, while a third is bound to protein (especially albumin), and the rest is bound to low molecular weight anions.

Magnesium is an intracellular ion, and there is only a small correlation between serum and intracellular concentrations of magnesium, probably because only 1% of the body's magnesium store is found in the blood *[Saris 2000, 3]*. Serum magnesium tests measure short-term intake variations, but they do not reflect the body's magnesium store. The magnesium concentrations in erythrocytes, mononuclear cells, and granulocytes also do not reflect the body's magnesium store because magnesium is primarily concentrated in muscles and bones *[Saris 2000; Arnaud 2008, 4]*.

Physiological Magnesium functions

Magnesium has a variety of functions, including acting as a cofactor for sodium and potassium ATPase, which is responsible for maintaining muscle membrane potential and action potential propagation. Magnesium deficiencies can result in muscle weakness and cramping *[Saris 2000]*. Adults who received moderate physical training supplemented with magnesium

showed improved cardiorespiratory function during a 30-min submaximal exercise test. These findings suggest a potentially beneficial effect of magnesium supplementation on muscle metabolism. Supplemental magnesium improves strength and muscle metabolism.

Asthma prevalence has increased dramatically over the last 50 years *[Chadwick 1997, 5]* maybe also due to a lower magnesium intake. Epidemiological evidence indicates that low magnesium intake is associated with airway hyper-reactivity and self-reported wheezing *[Britton 1994, 6; Soutar 1997, 7]*. Recent reports show that before industrialization, magnesium intake was estimated in 475–500 mg/day *[Altura 1991–92, 8]*. However, magnesium intake has declined substantially during the last century. Current dietary surveys show that the average magnesium intake in Western countries is often below the Recommended Drug Allowance which is 280 mg for female and 350 mg/day for male adults *[9]*.

Magnesium deficiency

Deficiency symptoms usually occur in conjunction with additional disease states, which contribute to the deficiency of magnesium. For example cystic fibrosis patients often have magnesium deficiency *[Foucard 1991, 10; Gupta 2007, 11]*. Symptoms of magnesium deficiency are associated with physiological interferences including nausea, muscle weakness, irritability, mental derangement and myographic changes. Hypokalemia and hypocalcaemia may also occur, since magnesium is active in potassium and calcium haemostasis *[NRC, 1989]*.

Causes for a magnesium deficiency are:

1) gastrointestinal tract abnormalities associated with malabsorption
2) excessive fluid and electrolyte losses
3) renal dysfunction with defects in cation reabsorption
4) general malnutrition and alcoholism
5) iatrogenic causes such as nasogastric suctioning
6) intravenous or intra gastric feeding of mixtures deficient in magnesium
7) use of drugs that interfere with magnesium conservation

Suboptimal Magnesium supply

The human body is always in a dynamic state meaning that means that continuously all organic matters are replaced and there is always a turnover of proteins, fats, carbohydrates, as well as a slower replacement of structures such as bones, taking place in living organisms. Enzymes are no exception; thus, there is a continual need for the raw materials, such as amino acids and minerals from which new enzymes can be produced. This turnover of minerals illustrates the continuous need for mineral intake. When minerals are in short supply due to insufficient food or when they are in poorly absorbed forms, humans usually do not die unless the deficiency is acute or prolonged. Instead, the person performs at a level that is less than his genetic potential. Pregnancy is a physiologic state of low serum magnesium compared with non-pregnant women *[Cunningham 2005, 12]*. Shortage of magnesium may be one of the causes for leg cramping during pregnancy.

Magnesium supplementation

Magnesium supplementation and the rate of how much magnesium is absorbed depend on many parameters such as dosage, delivery form, diet etc.

Magnesium absorption is negatively influenced by different parameters, such as

- Low protein intake
- Excess dietary fat
- Incorrect gut pH
- Precipitating anions such as Phosphates, Phytates, Oxalates
- Competitive with other minerals for absorption (high calcium intake)

Different Magnesium forms

Many different forms of minerals have been used and tested for mineral supplementation, which can be divided more or less into four different categories

Inorganic insoluble salts	Oxides (MgO), Carbonates ($MgCO_3$), Hydroxides ($Mg(OH)_2$)
Inorganic soluble salts	Chlorides ($MgCl_2$, Sulfates ($MgSO_4$)
Organic soluble salts	Citrates (Mg-Citrate), Lactates (Mg-Lactate), Gluconates
Organic soluble complexes	Bisglycinates (Mg-Bisglycinate, Zink-Histidine

Absorption of magnesium from different magnesium forms

Literature data on the bioavailability of various Mg forms provide scarce information on the best Mg salt to be used in animal and human supplementation. Most magnesium salts are poorly absorbed and may magnesium forms and high magnesium dosages worsen diarrhea and stomal output *[Nightingale 2001, 13]*. Magnesium absorption depends on different factors that determine how fast the magnesium is available in the gut for absorption and which transport channel is used then for magnesium absorption. Finally the magnesium level in the blood plasma also interacts with the magnesium pool in our body. If our magnesium stores are empty our body starts to up-regulate the

magnesium absorption and renal re-absorption.
At the present time the average intake of magnesium as RDA for healthy people is set at around 200–400 mg magnesium per da *[Anke 2006, 14]* which are relatively low amounts compared to the stone age where people consumed around 1200 mg magnesium per day *[Eaton 1996, 15]*. A good regulatory system in our human ensures the survival with only 200–400 mg magnesium by an intestinal active transport and an optimized renal re-absorption system.

Factors for magnesium absorption

- Status of magnesium stores in the body
- Type of magnesium form (inorganic, organic or complex (chelated) magnesium)
- Formulation (capsule, tablet or granule, slow release, liquid etc.)

The water solubility plays an important role for magnesium availability for absorption and the kinetics of magnesium absorption and excretion. Any increase in magnesium plasma level due to increased magnesium absorption is largely balanced by increased urinary excretion.
Magnesium absorption occur by a saturable carrier-meditated process and simple passive diffusion.
A third pathway for magnesium absorption is the active absorption of magnesium chelate in intact form via the dipeptide channel *[Schuette 1994]*.
Magnesium absorption is not regulated in the same way as for other minerals such as calcium. Compared to calcium, magnesium is much less absorbed at intakes above 8 mEq/meal, apparently due to greater restriction of intestinal permeability to magnesium *[Fine 1991]*.

Absorption of inorganic magnesium forms

Inorganic and almost water insoluble magnesium forms such as Magnesium oxide (MgO), Magnesium carbonate ($MgCO_3$), or Magnesium hydroxide ($Mg(OH)_2$) first have to be solubilized by strong acids in the stomach such as hydrochloric acid. This acid will convert the insoluble magnesium forms into Mg2+ ions that are then released into the gut for absorption. This conversion process takes time and requires an optimal digestive system. People with impaired digestive systems such as patients after ileal resection excrete twice the amount of insoluble magnesium salts such as MgO and less organic salts such as Mg-Citrate with their feces *[Schuette 1994]*.

Absorption of soluble magnesium salts

Soluble magnesium forms are mostly inorganic or organic salts that more or less dissolve in water and both forms set Mg2+ ions free in water that can be absorbed by the two pathways mentioned above: active channel mediated transport or simple diffusion. All these salts follow the same pathways and normally we could expect that the anion would not play a role for magnesium absorption, but differences were found depending on which anion was used *[Coudray 2005, 16]*:

- Fecal Magnesium excretion: 0.62 and 0.89 mg (35–50% of the given oral magnesium).
  - Highest fecal excretion: $MgSO_4$ and $MgCO_3$
  - Lowest fecal excretion: organic Mg salts, Mg gluconate and Mg aspartate

  There was a significant difference in Mg excretion between rats receiving the Mg gluconate and rats receiving MgO, $MgCl_2$, $MgSO_4$, $MgCO_3$ and Mg-Acetate.
- Magnesium Absorption: 0.92–1.22 mg (25–32% difference).
  - Lowest absorption: $MgSO_4$ and $MgCO_3$
  - Highest absorption: Organic Mg salts, in particular Mg gluconate

  There was a significant difference in Mg absorption between rats receiving the Mg gluconate and rats receiving MgO, $MgCl_2$, $MgSO_4$, $MgCO_3$ and Mg-Acetate.
- Urinary Magnesium excretion: 0.20–0.33 mg
  - Lowest urinary excretion: MgO, $MgCl_2$, $MgSO_4$, $MgCO_3$
  - Highest urinary excretion: Organic Mg salts, in particular Mg gluconate and Mg pidolate

  There was a significant difference in urinary Mg excretion in the rats receiving Mg gluconate compared to all the other rats. Urinary Mg excretion: confirmed the absorption data
- Magnesium retention varied between 0.71 and 0.90 mg.
  - Lowest Mg retention: $MgSO_4$ and $MgCO_3$
  - Highest Mg retention: Organic Mg salts, in particular Mg gluconate and Mg lactate

In a study with rats 10 different inorganic or organic magnesium salts such as oxide, chloride, sulfate, carbonate, acetate, pidolate, citrate, gluconate, lactate or aspartate were compared. The Mg absorption values obtained varied from 50% to 67%. The organic Mg salts were slightly more available than inorganic Mg salts *[Lücker 1993, 17]*.
In several studies it was shown consistently that that magnesium from organic magnesium salts is more absorbed than magnesium from Mg-Oxide *[Lindberg 1990, 18; Mühlbauer 1991, 19; Firoz & Graber 2001, 20]*.
Firoz & Graber (2001) compared the bioavailability of magnesium from magnesium L-aspartate, magnesium L-lactate, magnesium chloride and magnesium oxide in 16 healthy human volunteers (8 males and 8

females; age 25-55 years old). The volunteers received 90% of the Magnesium RDA (Recommended Dietary Allowance ~300 mg). They found that the bioavailability of magnesium from magnesium oxide was around 2-fold lower than from other magnesium forms.

Magnesium Bioavailability

The bioavailability of magnesium from magnesium salts appears to be dependent on their water solubility. Organic salts of magnesium have the greatest water solubility and demonstrate a greater oral absorption and bioavailability compared to less soluble magnesium preparations such as magnesium oxide, magnesium hydroxide, magnesium carbonate and magnesium sulfate *[EFSA 2005, 21]*.

Magnesium absorption depends on the number of absorbable ions (for all salts) or number of absorbable magnesium complexes (for magnesium bisglycinate). Normally bioavailability is regarded as the amount of substance that is entering the bloodstream of the body's circulation and is therefore theoretically bioavailable for our body. For Magnesium we have here a different and more complicated situation. When magnesium plasma levels increase, also the urinary magnesium excretion increases, which brings the magnesium levels down again quite fast.

The faster and the higher the magnesium levels increase the faster it is excreted via the urine *[Lücker 1985, 22]*.

Lücker found that the absorption and the urinary excretion of drinkable magnesium citrate was faster than after taking the same amount of magnesium citrate in the form of chewable tablets *[Lücker 1985]*.

Lücker stated that the word of bioavailability has to be redefined for magnesium and should be changed into „therapeutic accessibility". After incorporation of magnesium supplements only the amount of magnesium that is staying longer in the system is therapeutically accessible for the body.

The relative absorbability and bioequivalence of magnesium amino acid chelate, magnesium citrate and magnesium oxide was compared with placebo in a randomized double-blind study in 51 healthy volunteers *[Walker 2003, 23]*. The study concluded that the organic forms of magnesium (citrate and amino-acid chelate) are more absorbable than magnesium oxide or placebo as assessed by the 24 hour urinary excretion after 60 days of daily supplementation *[Walker 2003]*.

Magnesium citrate was found to result in the greatest serum magnesium concentrations following both acute and daily supplementation *[Walker 2003]* but it was also shown that the magnesium from Magnesium citrate is also quite fast excreted again via urine *[Lücker 1985]*.

The magnesium that is entering the blood stream needs to be immediately attached to organic molecules in the body for example to DNA, Enzymes, ATP, or proteins such as Albumin. No matter what product is used, it must be taken over a long period, because magnesium remains only in the human body, if there are molecules that bind to the mineral.

One of the first biochemical adaptations that should be improved parallel to increased magnesium supply is the provision of sufficient amounts of binding molecules that also can be observed after about four weeks of magnesium supplementation *[Golf 2006]*.

A study by Hillman (1996) *[24]* indicates that mineral oxides such as magnesium oxide are less soluble than other sources of minerals and resist further digestion and they are usually less bioavailable than the more soluble and ionisable inorganic salts or organic soluble salts.

Magnesium bisglycinate is better and faster absorbed than magnesium oxide and magnesium bisglycinate was better tolerated than magnesium oxide *[Schuette 1994, 25]*.

Organic forms of minerals such as example citrates and glycinates are also often more bioavailable than inorganic salts such as chlorides or sulfates *[EFSA Statement 2008]*.

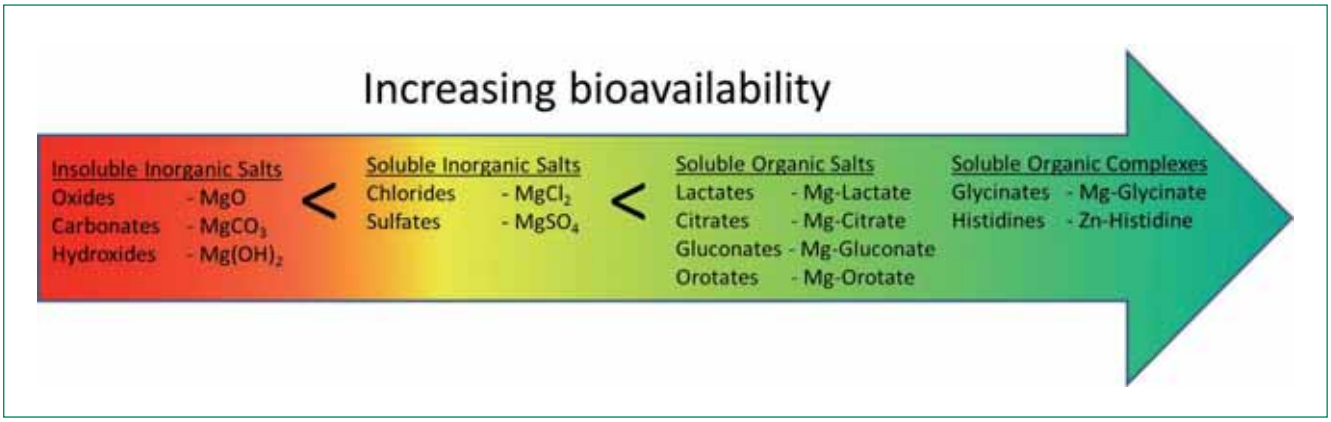
Amino acids have been used for a long time already to enhance bioavailability, stability and safety of minerals and trace elements in human nutrition. One very successful product that is sold in Germany since decades is zinc histidine as Curazink® (from Stada), where the amino acid histidine is used to form a zinc chelate and to enhance the absorption of zinc. Magnesium bisglycinate is available and popular in the US and Europe. In Poland one of the leading magnesium products in pharmacies is ChelaMagB6® (from Olimp Labs®) and uses Magnesium bisglycinate.

Already in 1966 Prof. Graff from Utah showed in rats that magnesium absorption is strongly enhanced by the chelation with dairy proteins *[Graff 1966, 26]*: Magnesium absorption from magnesium chelate was:

- 2.3 times greater than from magnesium carbonate
- 3.6 times greater than from magnesium sulfate
- 8.8 times greater than from magnesium oxide

Conclusions from all existing studies for best magnesium absorption:

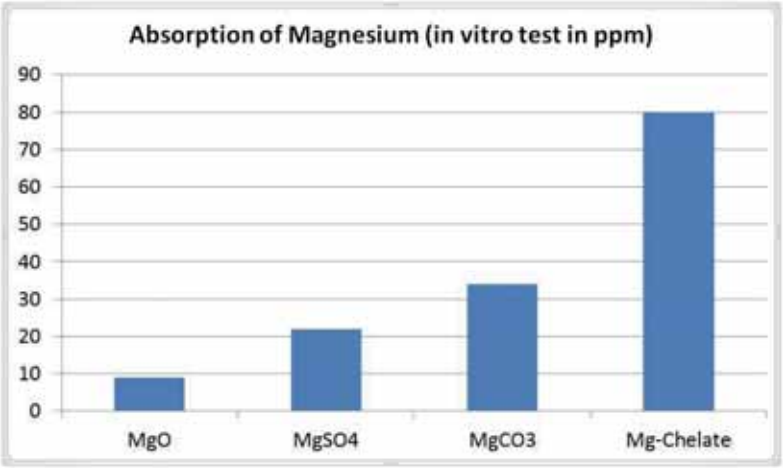
1. High Water solubility is beneficial for magnesium absorption
2. Magnesium Plasma levels are as important as magnesium excretion



Picture 1 *Schematic graph to show the different bioavailability of the different magnesium forms (created by Siebrecht 2013)*

3. Higher magnesium plasma levels lead to increased magnesium excretion
4. Urinary Magnesium excretion is a marker of magnesium retention
5. Higher amounts of Magnesium often lead to gastrointestinal problems
6. Lower dosages of Magnesium are better absorbed and less excreted
7. Better to take smaller amounts of highly bioavailable magnesium forms
8. To reduce a Magnesium deficiency it is best to take Magnesium supplement
   - at lower dosages (100–200 mg per serving)
   - several times a day (2–3 times)
   - for a longer period of time (3–6 months at least)

Based on all the facts that include data from magnesium plasma levels and magnesium excretion differences in the bioavailability of magnesium, following the new definition, can be visualized in the following picture 1.



Picture 2 *Absorption of different Magnesium forms in vitro (Graff 1966)*

Absorption pathways of minerals and chelates

Nutritive minerals that are supplied as soluble inorganic or organic salts will release their mineral ions in the low pH of the stomach and duodenum.

Calcium and Magnesium are absorbed from the intestinal lumen by two distinct and classical mechanisms, active transport of small amounts and passive diffusion of larger amounts of minerals, and their relative magnitude of importance is determined by the amount of free calcium or magnesium available for absorption:

1. Active transcellular absorption
   Active, transcellular absorption occurs only in the duodenum when calcium or magnesium intake is low. This process involves import of the mineral ions into the enterocyte, transport across the cell, and export into extracellular fluid and blood. Calcium and Magnesium enter the intestinal epithelial cells through voltage-insensitive (TRP) channels and are pumped out of the cell via a calcium-ATPase. The rate limiting step in transcellular mineral absorption is the transport across the epithelial cell, which is greatly enhanced by carrier proteins.

2. Passive, paracellular absorption (Diffusion)
   Passive, paracellular absorption occurs in the jejunum and ileum, and, to a much lesser extent, in the colon when dietary calcium and magnesium levels are moderate or high. In this case, ionized calcium diffuses through tight junctions into the basolateral spaces around enterocytes, and hence into blood.
   Tight junctions (English „tight connection", lat zonula occludens) are narrow strips of membrane proteins, that the epithelial cells of vertebrates completely encircle and that are in close contact with the bands of the neighboring cells. In this way the tight junctions close the cell gap

to form a paracellular barrier, called diffusion barrier, which controls the flow of molecules through the epithelium. They also have the task to maintain the polarity of epithelial cells: They prevent the diffusion of membrane components from the apical region laterally and vice versa. When calcium and magnesium availabilities are high, this pathway is responsible for the bulk of calcium and magnesium absorption, due to the very short time available for active transport in the duodenum.

3. Active absorption of chelates via the di-peptide channel
   Beside the classical two pathways of mineral absorption there is a potential third mechanism of how minerals can be absorbed. Cationic minerals must be chelated by proteins in the cell wall prior to absorption. This endogenous chelating process is slowing down and limiting the absorption process. If bisglycinates are used in oral supplementation there is no additional chelation of the mineral required at the brush border of the cell membrane so the membrane transport is more rapid *[Kirchhoff 1983, 27]*.
   The reason is that the Bisglycinates are directly absorbed and transported via the di-peptide channel that is normally used for protein peptide absorption.

The absorption of minerals presented as Amino Acid Chelates such as bisglycinates is therefore more effective than minerals that are present in the cationic state coming from inorganic or organic salts due to their direct absorption via the di-peptide channel. The human intestine contains much more di-peptide carriers that enable protein absorption then ionic mineral receptors which is the reason why Amino Acid Chelates can be absorbed faster and at a higher rate than ionic minerals.

The mechanism of bisglycinate absorption was intensively studied for ferrous bisglycinate. Due to the similarity in structure, it is expected that magnesium bisglycinate, like ferrous bisglycinate, will be handled similarly to other bisglycinates.

Following oral administration, ferrous bisglycinate joins with the intestinal intraluminal pool of inorganic, non-haem iron, and is absorbed intact into the mucosal cells of the intestine, and is subsequently hydrolysed into its iron and glycine components. It is expected that magnesium bisglycinate would be absorbed into the mucosal cells similarly intact and would subsequently be hydrolysed into magnesium and glycine components.

In the study by Bovell-Benjamin 2000 in the United States, the absorption of iron from ferrous bisglycinate was compared with its absorption from ferrous sulfate. Both sources were fed to the same ten iron-deficient men in a whole-maize porridge with high phytate content. The purpose was to determine if ferrous bisglycinate protects the absorption of iron from inhibition by phytate and whether the bisglycinate iron exchanges with ferrous sulfate iron in the intestinal pool. In the first experiment the two sources of iron were fed separately on two consecutive days, and in the second the iron sources were fed together in the same meal.

Each iron source was labeled with a different isotope. Had the iron bisglycinate (Ferrochel®) degraded in the intestine and its iron exchanged with the ferrous sulfate iron, the observed absorption of iron from the two sources would have been identical owing to mixing of the free iron isotopes in the intestinal lumen.

When the two iron sources were fed in two separate maize meals, however, iron absorption from the bisglycinate was five to six times higher than from the ferrous sulfate (on average, approximately 6-7% compared with 1-2%, respectively). This discrepancy persisted when the iron sources were mixed together in the same meal, indicating that there was no exchange of the isotopes from the two iron sources in the intestinal pool, and that the ferrous bisglycinate molecule was probably absorbed in an intact form.

Amino Acid Chelates (Bisglycinates)

Plants overcome the problems with the reactivity of minerals by using the method of creating mineral complexes, which is known as chelation. When humans consume plants and animals and use their various components for their own nutrition, most of the minerals ingested are presented in the form of natural chelates. This is the main reason why natural plant based minerals in organic form are much more bioavailable than inorganic mineral salts. Chelation, thus, is a safe and natural way for transporting needed mineral ions into living organisms. Amino acid chelates are in fact mimicking the natural delivery form of minerals from plants or animal sources and are closer to the "natural form" of minerals than the inorganic mineral salts.

Already in the 1960s, scientists developed the concept of chelating a metal ion prior to feeding minerals or trace elements to animals. The scientists believed in that time that by creating a bigger and neutral compound, they could protect the metal ions from being complexed with other insoluble salts within the stomach, which would render the metal unavailable for absorption.

Amino acids as chelating agents have a long history in mineral supplements. Since the early development of these compounds, much more research has been

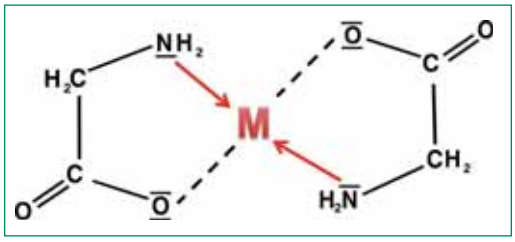
conducted, and has been applied to human nutrition products and in a similar manner also to animal nutrition experiments that pioneered the technology. Ferrous bisglycinate is an example of one of these compounds that has been developed for human nutrition and clinically studied.

Amino acids are effective metal binders and they were chosen as the prospective ligands, and research was conducted on the metal-amino acid combinations. The worldwide research since then supported the theory that the metal-amino acid chelates were able to enhance mineral absorption.

Naturally occurring amino acids can be used as ligands that confer both increased bioavailability and complete utilisability once within the body. Glycine is the smallest of all amino acids and it fulfills all requirements to create Amino acid chelates. Amino acid chelates must have the following properties to be used in human nutrition:

- must have a molecular weight under 800 Daltons to be absorbed
- must be electrically neutral, non-ionizing, and less reactive
- must have a proper stability constant – stays intact in the absorptive gut area
- must have an easy to metabolize ligand-better nutrient density
- must be more stable than the potential formation constants of ligands from classical foods
- must be stable enough to cross the intestinal cell membrane intact
- stability must be low enough for the cytoplasmic ligands to remove the metal in the mucosal cells

According to the Association of American Feed Control Officials (AAFCO), a metal amino acid chelate is defined as the product resulting from the reaction of a metal ion from a soluble metal salt with a mole ratio of one to three (preferably two) moles of amino acids. The average weight of the amino acids must be around 150Da and the resulting molecular weight of the chelate must not exceed 800Da.



Pict. 3 *Metal chelate complex with 2 molecules of glycine. 4 bonds (2 ionic and 2 coordinate covalent bonds = red arrows) form a tetrahedral structure and 2 binding sites are still free at the metal ion inside.*

$$Mg^{2+} + 2\ NH_2\text{-}CH_2\text{-}COO^- \Rightarrow Mg(NH_2\text{-}CH_2\text{-}COO)_2$$

Magnesium cation | 2 Glycinate anions | neutral Magnesium bisglycinate

Pict. 4 *Formation of magnesium bisglycinate from magnesium cations and glycinate anions*

Chemically, chelates are a combination of a metal ion with a chemical compound to form two heterocyclic rings with the metal ion as the closing link and the connection of the rings. Bisglycinates are neutral components and the positive electric charge of the metal ion is neutralized by the two negative charges from the glycinate, following the equation (Pict. 4).

That magnesium bisglycinate is a neutral complex is an important fact because these neutral components can move freely through the cells without following the osmotic gradients the metal ions usually have to follow as ions. As neutral complexes these mineral ions also do not disturb the mineral and ion balance within the cells. Neutralized metals are also less active than the free metal ions. In magnesium bisglycinate the polyvalent mineral cation (M = magnesium) is attached to the amino acid glycine by 2 ionic bonds (black) and 2 coordinate bonds (red arrows) in such a way as to form heterocyclic 5 member rings with the mineral (M) being the closing member of each ring. Metal Ions always have 6 binding sites. In magnesium bisglycinates only 4 of the 6 binding sites are blocked by glycine and two more sites are free for water molecules or enzymes to attach to the complex.

These two free binding sites are one of the reasons why magnesium bisglycinate is easily soluble in water and that the magnesium complex can be destroyed again by enzymes that attach at the free binding site.

A large variety of compounds have been examined as potential chelating agents (or ligands) of metals to potentiate absorption. These include organic acids, sugar acids, amino acids, larger organic polymers and synthetic chelating molecules *[Kratzer and Vohra, 1986b, 29]*. Chelating ligands must be chosen to bind metals sufficiently to withstand gastric cleavage and promote better absorption, but not be bound so strongly as to resist cleavage once they are absorbed. Ligands that have conferred excellent properties of both increased bioavailability and being totally utilisable once within the body are the naturally occurring amino acids which are the building blocks of proteins and enzymes and certain vitamins. Such chelates provide advantages over other synthetic ligands, such as Ethylene-Diamine-Tetra-Acetic acid (EDTA), where it has been observed that the ligated material occurs intact in human urine or alternatively ligated to and therefore removing other essential elements from the body *[Pineda 1994]*.

EDTA

During the discovery of chelates also synthetic chelates were developed. An example of such a synthetic is Ethylene-Diamine-Tetra-Acetic acid (EDTA). EDTA is a synthetic amino acid and chelating agent for divalent metals. EDTA is essentially insoluble in water, and will only dissolve when it is neutralized with sodium hydroxide to a pH = 8.0. EDTA is forming 1:1 complexes with metal ions where all 6 binding spots are blocked by the EDTA. That means that there is no spot for water or other molecules left to bind and to dissolve or destroy the complex.

The synthetic amino acid EDTA is therefore a very strong metal chelator and can create metal-chelate-complexes that are often too stable and not nutritionally viable. EDTA is so effective in binding the magnesium that it makes it completely unavailable also for enzymes. Most enzymes that synthesize or modify nucleic acids (e.g. polymerases, ligases, kinases, nucleases) are Mg2+-dependent and their activity can be completely blocked by the addition of EDTA. Another disadvantage of EDTA is when the mineral is taken away from the EDTA complex, the ligand EDTA cannot be used by the body and is excreted.

During the expulsion process the EDTA ligand will randomly chelate and strip another metal ion which is then excreted by the body *[Ashmead 1993,30; Pineda 1994, 31]*. EDTA is therefore only used in medicine to remove heavy metals, such as lead or mercury from the bloodstream by the formation of very strong chelate complexes that are then excreted via the urine.

Amino acid chelates provide advantages over synthetic ligands, such as EDTA because the amino acid chelates are stable enough during digestion and absorption but the body cells are able to destroy these amino-acid chelate complexes and separate the amino acids and the minerals from each other and use both separately.

Both, amino acids and the minerals inside the chelate complex are of nutritional value for our body and are used by our body. Therefore amino acids chelates are physiological active chelates and they absolutely not comparable with the more chemical, synthetic and non-physiological EDTA chelates. Due to its properties pure EDTA is not permitted to use in food supplements and PARNUTS, and Ferric Sodium EDTA is the only allowed EDTA complex in Europe for human nutrition.

Other organic magnesium salts

There are other organic magnesium salts available such as magnesium orotate, magnesium lactate and magnesium citrate.

These are pure organic acid salts that do not contain a nitrogen atom and form the classical organic salts.

The structural differences of these organic acids to alpha amino acids determine that they are not able to form water stable complexes.

Orotate, lactate and citrate mineral salts are handled in the same way by our body than all the other inorganic or organic magnesium salts such as magnesium chloride or magnesium sulfate.

When these organic magnesium salts get in contact with water they are completely separated and ionized so that the magnesium ion is surrounded by 6 water molecules at all 6 binding sites.

At this point all the magnesium salts have the same metabolic fate. They are transported to the mucosa cells where they have to be chelated by proteins to be transported through the cells. The reason why alpha amino acids such as glycine form stable metal complexes is on one hand that they contain a nitrogen atom with a free pair of electrons that has a high affinity to form coordinate covalent bonds.

On the other hand this nitrogen atom is in alpha position, which not too far away from the carboxyl-oxygen to form a 5-ring closed by the metal ion inside.

Production of Bisglycinates

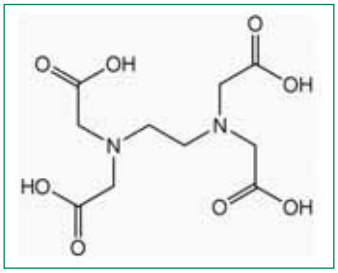
An important fact is that bisglycinate chelates are the product coming from a chemical reaction and are not partially chelated compounds with a mix of unbound and inorganic magnesium ions. Bisglycinates cannot be obtained by either a simple powder mix of magnesium oxide and glycine or mixing of magnesium salts with other hydrolysed protein sources such as soy protein hydrolysates.

Bisglycinate chelates are the product resulting from the chemical reaction of a metal ion from a soluble metal salt with amino acids with a mole ratio of one mole of metal to one to three (preferably two) moles of amino acids to form coordinate covalent bonds.

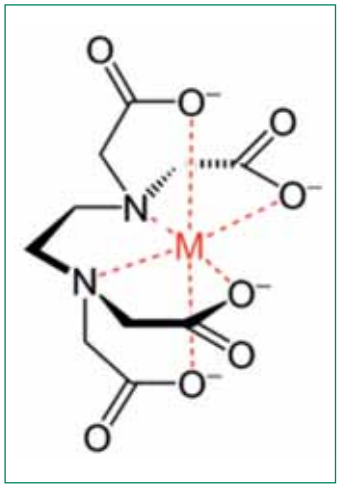
That glycine and magnesium really form a bisglycinate complex was proven by x-ray analysis of the crystals by the American company Albion, which also holds many patents on the production method of different chelate-mineral complexes.

Albion also patented a method to analyze mineral chelates in dry form by using "Fourier Transform Infrared (FTIR) Spectrometry" to determine the presence of a chelate and how much of the product is chelated. This unique process identifies the molecular bonds indicating chelation.

The US Patent #7,144,737, „Process for Determining the Percent of Chelation in a Dry Mixture," was awarded to Albion on December 5, 2006.



Pict. 5 *Chemical structure of EDTA*



Pict. 6 *Chemical structure of a 1:1 EDTA-Metal-Complex. All six possible positions are blocked by EDTA. There is no free binding space for water to bind and to dissolve this complex.*

Magnesium Bisglycinate

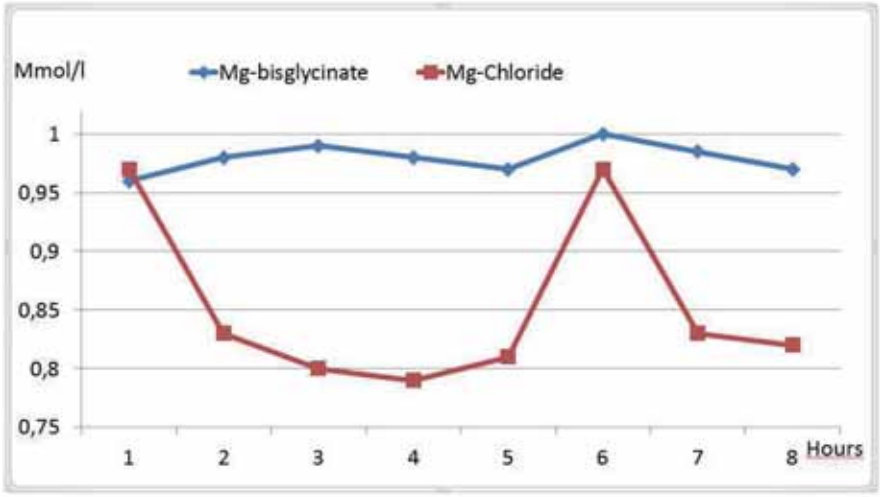
The magnesium content in of magnesium bisglycinate differs from 8–18% magnesium. Magnesium bisglycinate is freely soluble in water. Magnesium bisglycinate provides increased intestinal absorption and bioavailability of magnesium in the bisglycinate form.

Benefits of magnesium bisglycinate

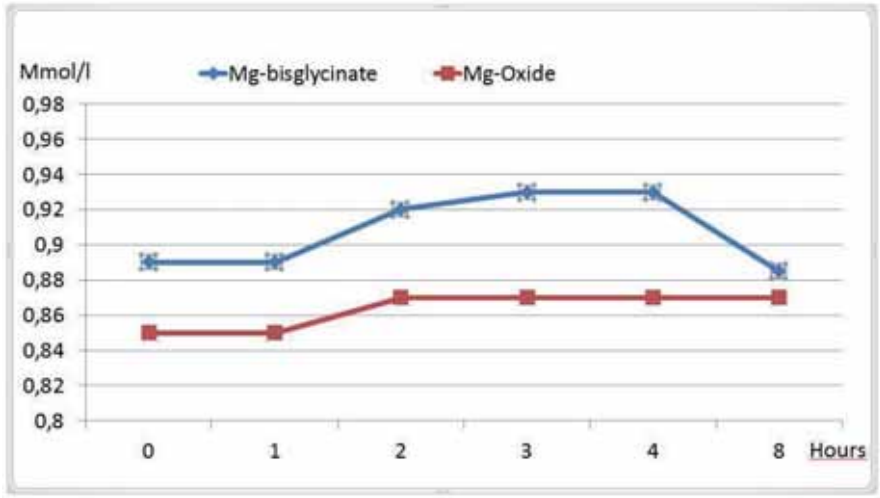
Metal ions are often catalysts for many chemical reactions and can interact with other ingredients such as vitamins or with oxygen in products such as food or dietary supplements. Bisglycinate salts are stable products in dry form and increase also the stability of powder blends. The stability of the chelated products was demonstrated by a lack of interaction between the metal amino acid chelates and any of the components of the blend with other ingredients, including the vitamins *[Ashmead 1995, 32]*.

Magnesium bisglycinates offer a number of advantages of administering magnesium to humans over other inorganic or organic metal salts occur including:

1) optimal intestinal absorption of the mineral
2) less competition with other minerals such as calcium for example
3) protected from binding and precipitating dietary phosphates, phytates, tannins, and roughage
4) less competition from metals vying for the same transport sites in the small intestine
5) avoidance of suppressed absorption, due to some ionic elements being out of proportion to others also required for nutrition
6) reduction in digestive irritation and toxicity



Pict. 7 *Comparison of the absorption of Mg-bisglycinate versus mg-Chloride (Abrahams 2001)*



Pict. 8 *Bioavailability of Mg-Oxide versus Magnesium bisglycinate*

Chelates increase the mineral bioavailability

A study by Hillman (1996) indicates that e.g., mineral oxides are less soluble than other sources of minerals and resist further digestion. They are usually less bioavailable than the more soluble ionisable inorganic salts. Organic forms of minerals are often more bioavailable than inorganic salts. The naturally occurring amino acids are ligands that confer both increased bioavailability and complete utilisability once within the body. Amino acid chelates provide advantages over other synthetic ligands, such as EDTA, where it has been observed that the ligated material occurs intact in human urine or alternatively ligated to essential elements in the body, which can lead to the unnecessary removal of these essential compounds *[Pineda 1994, 33]*. Several studies show that Amino acid chelates are better absorbed than many other mineral sources *[Heaney 1990, 34; Pineda 1994; Bovell-Benjamin 2000, 35]*.

Chelates protect the Magnesium in the human intestinal tract

While in the chelated state, the magnesium ion is protected by the tetrahedral bonding configuration of the chelating ligands from irreversibly combining with dietary phosphates, phytates, tannins and roughage and becoming unusable for nutrition.

Chelates tower the risk for osmotic diarrhoea

In the chelated state the magnesium ion is neutral and does not add osmotic pressure like other ions to the intestinal electrolyte status. Too many ions in the intestine would increase the osmotic pressure that would cause a flow of water into the intestinal lime to dilute these ions and too lower their concentration with the consequence of forming lose stools or the development of diarrhoea. This cannot happen with Magnesium-Bisglycinate and is the main. Taken on empty stomach (600 mg Mg/day) magnesium bisglycinate is half as reactive (hypoacidity) compared to magnesium citrate and has a much lower laxative effect than magnesium citrate. So especially for high dosages Magnesium bisglycinate is the better choice

for people that are sensitive to develop osmotic diarrhoea.

Mineral chelates do not compete with other mineral ions

In the chelated state Magnesium does not compete with all other ions in the lumen for the ionic absorption pathway, because Magnesium bisglycinate is absorbed independently from other minerals and metal cations via the dipeptide absorption channel.

Chelates are directly and faster absorbed

All other magnesium forms set magnesium ions free in water and in the intestine ionized magnesium is what is most likely to cause the bowel intolerance symptoms like diarrhea or very soft stools which then makes magnesium deficiency worse. Ionic magnesium from all other salts has to be chelated in the small intestine cells before it can be absorbed into the mucosa cells. Therefore other proteins or amino acids are needed to form in situ chelates with magnesium. Magnesium bisglycinate is already in the chelated state and can be absorbed directly by the intestinal cells. No further protein or chelation is needed to absorb magnesium bisglycinate. The Glycine-to-magnesium bonds in magnesium bisglycinate are sufficiently strong to predominantly pass through the stomach and the acidic portion of the small intestine (duodenum) intact and still protecting the metal from these unwanted reactions.

Magnesium bisglycinate retains enough of the character of a dipeptide so that it bypasses the duodenal receptors that take up inorganic metal ions and instead is absorbed at peptide and amino acid receptor sites that are predominant in the jejunal portion of the small intestine.

Dosage of Magnesium bisglycinate

The RDA of magnesium is set at 300–350 mg per day. Today many magnesium products offer 100% of the RDA in one serving and dosages for magnesium of 300–400 mg or more per serving are available.

Some people still believe that higher dosages necessarily are more effective than lower dosages. Fine (1991) tested the absorption of 8 different magnesium dosages in normal, healthy humans. who received 0, 10, 20, 40, and 80 mEq of magnesium acetate. Although the total magnesium absorption increased with each dosage, the relative magnesium absorption fell progressively from 65% at the lowest dosage to 11% at the highest intake *[Fine 1991, 38]*. These results are statistically show that the magnesium absorption process simultaneously uses a mechanism that reaches an absorptive maximum plus a mechanism that endlessly absorbs a defined fraction (7%) of ingested magnesium. This means from 10 mEq magnesium given 6,5 mEq (=65%) are absorbed but if 8 times the amount of magnesium is given (=80 mEq) only 8,8 mEq are absorbed and 71,2 mEq of the magnesium = 89% are excreted with the feces and this increases the risk for diarrhea and gastrointestinal discomfort.

The German health Institute for risk management (BfR) found that the oral supplementation soluble magnesium salts of more than 360 mg per day can cause diarrhea (BGVV 2002). Dosages of 250 mg of magnesium per day or lower did not cause such effects *[SCF 2001]*. The European Commission therefore set the „No Observed Adverse Effect Level (NOAEL)" for magnesium at 250 mg/Tag for the additional supplementation of magnesium in the form of soluble magnesium salts. They also used the safety factor of 1 and set the „Tolerable Upper Intake Level (UL) von 250 mg/day *[SCF 2001, 39]*. Today the advice of the German and European authorities is to take not more than 250 mg of magnesium per day and to divide this dosage into 2–3 portions, which means 80–100 mg per serving.

Evidence also shows that the active absorption of minerals to is highly regulated in inverse proportion to the concentrations of the respective minerals in the bod *[Bovell-Benjamin 2000]*. That means if we are low in magnesium and the content of magnesium is low in the intestine the active absorption rate is much higher than if we have higher magnesium levels in our body and the concentration in the intestine is high. Low dosages magnesium are actively much better and more effectively absorbed than higher dosages. High dosages of magnesium given at once also cause diarrhea quite often, which is a sign that the majority of the magnesium was not absorbed but immediately excreted via the feces.

Disadvantages of high magnesium dosages

Good soluble mineral salts released the mineral ions immediately are and given in high dosages the active transport mechanism for these minerals is overloaded and mostly passive diffusion happens in the jejunum and ileum, but the rate of mineral absorption there is extremely low and the majority of the given dosages cannot be absorbed. Released mineral ions also may unite with free phosphates, phytic acid, tannins or dietary roughage common to the intestinal lumen and precipitate out of usefulness as dietary mineral sources *[Kratzer and Vohra, 1986a, 40]*. Several minerals and their ions compete in the intestinal tract for the same sites of absorption where one type of metal ion suppresses the potential absorption of the other ones *[Dyer, 1969, 41]*.

Advantages of low mineral dosages

As the study from Fine 1991 showed, lower dosages of magnesium absorbed much better and much more

efficient than higher dosages. A similar example we see with haem iron which is a porphyrin ring chelate of iron and is preferentially absorbed over other forms of iron, even when it is given in lower concentrations relative to other iron sources in the same dosing *[Hillman, 1996]*. The same effect we see here with magnesium bisglycinate: Low dosages of magnesium bisglycinates are more effectively absorbed than higher dosages of other magnesium sources and already have an impact on some physiological parameters even at low dosages.

Effectiveness of magnesium bisglycinate

It was shown that even small dosages of magnesium are efficient if given in the highly bioavailable form of magnesium bisglycinates. 500 mg magnesium bisglycinate (=80 mg magnesium) given twice daily was able to decrease platelet adhesiveness and increased thrombin clotting time even better than Omega-3 fatty acids *[Weaver 1988, 42]*. Important to know here is that the plasma levels of magnesium did not increase but the urinary excretion of magnesium increased showing that the magnesium was really absorbed, reached the blood stream and was excreted. Also the potassium content in the erythrocytes increased demonstrating the potassium sparing effect of magnesium. There have been mixed results in studies of magnesium treatment of leg cramps in pregnancy with magnesium lactate/magnesium citrate when compared with placebo. Some studies found positive effects, but other studies did not find any effect of magnesium lactate/magnesium citrate on both, frequency and intensity of leg cramps in pregnant women *[Nygaard 2008, 43; Dahle 1995, 44]*. Magnesium bisglycinate has shown to be effective in the treatment of leg cramps in pregnancy *[Supakatisant 2012]*.

Glycine, a beneficial chelating agent

The organic acids that are used in other organic magnesium components such as citrate, lactate, orotate, gluconate are highly bioavailable, but they are just used by the body as another energy source and are converted by the citric acid cycle quite quickly. The amino acid glycine used in magnesium bisglycinates offers some other nutritional benefits as well because it is one the 22 amino acids that build our body structures. Glycine has many important metabolic functions in the human body. For example, glycine is used to form collagen, a key protein in cartilage and connective tissue and it helps to preserve muscle mass. It is an essential component in the synthesis of creatine, it helps to prevent liver damage *[Yin 1998, 45]* due to alcohol abuse, and prevents ulcer-formation. Glycine also plays important roles in the central nervous system (CNS), the immune system, energy production, and the maintenance of a healthy prostate. Glycine is also part of the body-own tri-peptide Gluthathion which is one of the strongest anti-oxidants in our body. Glycine has also shown to have significant anti-ulcer and cytoprotective properties against chemically induced gastric ulcers *[Tariq 1997, 46]*.

Glycine also protects against chemically induced damage from components like chlorpromazine, Cisplatin and other hepato *[Rose 1997, 47]* or nephro toxic agents. Glycine is a good and safe nutritionally functioning chelating agent. Glycine is the smallest amino acid and thus, forms mineral chelates of the smallest possible molecular weight which is important for great absorption potential. The stability constant that glycine possesses is excellent, as well. It allows for the chelate to remain intact throughout the pH range of the gastrointestinal tract, but it is not too strong - allowing for the efficient release of the minerals to the biological tissues in need of them. Dietary glycine was found to be a safe and effective treatment to reduce the nephrotoxicity of cyclosporines *[Thurman 1997, 48]*. A Glycine diet (5%) was shown to totally prevent mortality and reduce liver and lung injury in animals exposed to endotoxin shock *[Ikejim 1996, 49]*. Glycine minimizes alcohol-induced liver injury by preventing ethanol from reaching liver by activating first-pass metabolism in the stomach *[Limuro 1996, 50]*.

Safety of magnesium bisglycinate

Bisglycinates are safe and allowed nutrients and are used in many countries worldwide already since decades. The European Food Safety Agency has allowed bisglycinates as delivery form for minerals and trace elements in the EU for zinc, copper, iron, calcium and magnesium, manganese. Magnesium bisglycinate has an excellent safety profile so that it can be used also in children and pregnant women. In the past magnesium bisglycinate was already used in children to treat asthma *[Gontijo-Amaral 2007, 51]* or cystic fibrosis and in pregnant women to treat leg cramps *[Supakatisant 2012, 52]*.

Magnesium bisglycinate has an oral LD50 value of 5,220 mg/kg body weight in rats, corresponding to 522 mg magnesium/kg body weight. Due to the similarity between magnesium bisglycinate and ferrous glycinate, it is expected that magnesium bisglycinate would have similar or better relative results in similar toxicological studies (since magnesium is a macronutrient, whereas iron is a micronutrient) and that no toxicologically significant impact would result from administration of magnesium glycinate at the respective dosage levels and forms of administration anticipated for magnesium.

On the basis of the available bioavailability, and toxicity data with magnesium bisglycinate, in combination with the safety evaluations provided by EFSA for ferrous bisglycinate (EFSA, 2006) and for copper, zinc,

calcium, magnesium bisglycinates (EFSA The EFSA Journal (2008) 718, 1-26) and for manganese (The EFSA Journal (2009) 1114, 1-23) and the SCF safety evaluation of other magnesium sources (SCF, 2003), no safety concern should arise from the proposed use of magnesium bisglycinate, meeting the specifications prepared herein, as a direct replacement for permitted magnesium forms in food supplements (Council Directive 2002/46/EC), and fortified foods and all the categories of PARNUTS (Council Directive 89/398/EEC) other than for baby foods and infant formula.

One fact that underlines the safety of magnesium bisglycinate is that the „Polish Gynaecological Society Expert Committee" gave their recommendations regarding the application of Chela-Mag B6® in obstetrics and gynaecology in Poland *[Bilinska 2011, 53]* and also the health institute for mother and child gave the advise to take Chela-Mag B6 to mothers and pregnant women *[Instytut Matki i Dziecka 2010, 54]*.

Regulatory of Bisglycinates in Europe

The amino acid glycine (synthetic or natural) is already permitted in the EU for use in foods on substances that may be added for specific nutritional purposes in foods for particular nutritional uses *[PARNUTS 2001, 55]*. Glycine and its salts (E640) have an ADI that is not specified and are permitted as food additives *[56]*. The EFSA has already evaluated and accepted the safety of the amino acid chelate part (glycine) in metal glycinates by the AFC Panel in 2006.

The EFSA panel agrees that the subchronic studies on ferrous bisglycinate can be used to assess the subchronic toxicity of the glycinates. From the studies a NOAEL of 500 mg/kg body weight/day for ferrous bisglycinate in rats (the highest dose tested) was derived, corresponding to approximately 400 mg glycinate/kg body weight/day. The European food and safety agency (EFSA) has published an opinion about bisglycinates which consist of two molecules of glycine that are linked to a bivalent metal ion, namely Cu+2, Zn^{+2}, Ca^{+2}, and Mg^{+2} *[57]*, Mn^{+2} *[58]*. The EFSA evaluated the safety of bisglycinate chelates of copper, zinc, calcium, magnesium as sources of the minerals as nutrients and also checked the bioavailability of the mineral cations from these sources.

The EFSA also received data regarding the bioavailability of the different minerals from their sources, showing that the minerals are bioavailable after oral administration. The EFSA stated in this opinion paper that the mineral amino acid chelates are intended for use as a direct replacement for the permitted respective mineral forms for:

copper	in foods for nutritional purposes in food supplements according Council Directive 2002/46/EC
calcium und magnesium	in foods for nutritional purposes in food supplements for the categories of foods for particular nutritional uses (PARNUTS) other than for baby foods and infant formula according to Council Directive 89/398/EEC
zinc	in foods intended for the general population (including food supplements) in foods for particular nutritional uses (PARNUTS)

A conservative estimate of the dietary exposure was made based on a hypothetical intake from all sources (PARNUTS, food supplements and foods intended for the general population) to estimate the tolerable upper intake levels

Copper	5 mg/day	Copper bisglycinate	12 mg glycine/day
Zinc	25 mg/day	Zinc bisglycinate	57 mg glycine/day
Calcium	2.500 mg/day	Calcium bisglycinate	9.239 mg glycine/day
Magnesium	250 mg/day	Magnesium bisglycinate	1.523 mg glycine/day

TThe EFSA Panel noted that this estimated glycine exposure is safe and is much lower than the NOAEL of 400 mg glycinate/kg bw/day, the highest dose tested. In addition the normal (mean) intake of glycine in proteins from both food of animal origin, and vegetable origin was calculated to be about 26 mg/kg bw/day for adults (>15 years) and to about 43 mg/kg bw/day for children (< 15 years).

The safety and Maximum Tolerable Intake has been reviewed and evaluated by a number of distinguished scientific committees. These recommendations provide assurance that dietary supplementation with magnesium sources such as magnesium bisglycinate pose no safety concerns at these established levels, especially since the intended level of use of magnesium bisglycinate in foods, will not exceed those levels anticipated through existing magnesium supplementation and food fortification programmes currently used within the EU.

Furthermore following dissociation from magnesium bisglycinate, the free amino acid, glycine, will also be utilised in normal metabolic processes. Glycine (E640), poses no safety concerns since it is already permitted in the EU for use in foods under Directive 2001/15/EC of 15 February 2001 on substances that may be added for specific nutritional purposes in foods for particular nutritional uses (PARNUTS) *[EC, 2001]*. Glycine is also permitted as a food additive in the EU under Directive 95/2/EC on food additives other than colours and sweeteners *[EC, 1995]*.

Summary

Magnesium bisglycinates offer a number of advantages of administering magnesium to humans over other inorganic or organic metal salts. Studies have demonstrated the high bioavailability and safety of magnesium bisglycinate and efficacy even at lower dosages, which outperforms magnesium inorganic salts and some organic salts like magnesium citrate or lactate in certain applications.

It is expected that magnesium bisglycinate is absorbed in a different way than classical magnesium ions. Magnesium bisglycinate is absorbed intact via the dipeptide channels into the mucosal cells of the intestine, and is subsequently hydrolysed into its magnesium and glycine components.

The magnesium component of magnesium bisglycinate would then be handled systemically like any other source of magnesium. Magnesium bisglycinate also provides the amino acid glycine which might have additional amino acid benefits that all other organic acids or anions used for other magnesium components do not have.

Due to its high solubility at physiological pH and special chelated structure, magnesium bisglycinate maintains a high magnesium bioavailability in foods despite the presence of inhibitory factors. Bisglycinates such as Magnesium bisglycinate are acceptable food additives meeting appropriate food-grade specifications, and all are currently approved for use as food additives in the EU (European Parliament and Council Directive No. 95/2/EC of 20 February 1995 on food additives other than colours and sweeteners) and USA.

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