

## **BOOST YOUR IMMUNE SYSTEM** WITH NUTRITIONAL SOLUTIONS



### GLOBAL CONTEXT

The world's population is growing and life expectancy is longer than ever. At the same time, our environment has changed in a few decades, and our metabolism is at the same time confronted with more **stress**, **pollution**, and **less supply of essential nutrients** (due to intensive agriculture and animal farming, which have reduced the rate of nutrients available in food). In such a context, the question of preserving one's body and one's health is at the center of concerns.

It is observed that more than 4 out of 10 people in the world are now in a **proactive approach** to their health and well-being. An almost holistic approach including not only the practice of physical activity and a focus on a quality and balanced diet, but also a worldwide growing demand for food supplements, whether from young or old consumers. Regardless of the generation, one common theme when it comes to dietary supplements: **immunity**.

Only the physical form differs according to the generations: the oldest remaining attached to capsules and tablets, while the youngest favor gummies, chewable tablets and shots, in symbiosis with a more nomadic and more rushed lifestyle.

The growth of the dietary supplements for immunity market is estimated at 7% between 2014 and 2019, and is expected to explode from 2020 in response to the Covid-19 pandemic.



### **TAKING CARE OF ITS IMMUNE SYSTEM**

There are natural variations in the performance of the immune system between individuals, which are linked to : internal factors (age, sex, smoking habits, diseases – exposure to virus/ bacteria...), genetic variations (pollen allergies, diabetes...) but also external factors (environmental factors).

In particular, we know that adequate intake of vitamins and minerals is required for the immune system to function effectively. **A nutrient deficiency** decreases immune function by affecting both the innate and adaptive immune response, which leads to deregulation of the balance of the host's immune response, and **increases the risk of infection**. Nevertheless, the immune system can be swayed in the right direction with a diet which ensures that the metabolism is well equipped to defend itself against pathogens, allergens and other immune triggers. Western medicine has always been concerned with combating the pathogen once it has entered the body («pathogen directed therapy»), but now also recognizes that keeping the pathogen not so easily admitted is important. also (this is called "host directed therapy").

**Combined therapeutic approaches**, that is, combining pathogen control and hostdirected therapy, are now offered in cases of infection.

We will see in this «white paper» which nutrients have a proven effectiveness in immune function, and in what form they should be ingested to boost the immune system.



### **IMMUNE SYSTEM ALONG LIFE**

Every day, the human metabolism is exposed to factors that have the power to compromise its health: viruses, bacteria, but also stress, allergens, pollution ... contribute to a risk of infection.

The main function of the immune system is to protect our body from disease by recognizing and eliminating pathogens (viruses, bacteria), infected or cancerous cells, etc. Its corollary is the recognition of environmental antigens (food, airborne substances, etc.) as non-harmful: this is immune tolerance. When the human body perfectly fulfills these 2 roles, it is homeostasis. But if the immune response is overwhelmed, infections and diseases can occur. Also, poor immune tolerance can lead to allergic reactions and autoimmune diseases. The immune system **changes over the course of life**, and defense or tolerance problems can arise at any time.

In infants and children, the system being immature, infections are common as well as atopic disorders caused by hypersensitivity.

In adults, the immune response is mature with a large pool of memory cells. However, stressors can affect the balance and the body becomes more vulnerable to infections.

In older people, we talk about immunosenescence: many studies show that aging is accompanied by serious alterations in the immune system. It is for this reason that older people are more susceptible to infectious diseases such as the flu. The replication capacity of cells, the production of antibodies, the size of the population of memory T cells and the pattern of cytokine secretion are impacted by aging.

Throughout life, it is therefore important to ensure the support of its own natural defenses, so that the immune system is not prematurely impacted.

### INNATE AND ADAPTIVE IMMUNE SYSTEM

The role of the immune system consists in:

- Recognizing and maintaining what belongs to the metabolism
- Recognizing and reacting against abnormalities: Microorganisms, toxic substances, foreign
  matters, or internal infected celles, tumors

In humans, the immune system develops 2 different immune responses:

• The **innate immune system**: which is the first line of defense and provides an immediate effect, limited in time, by a **nonspecific** response to a pathogen.

This system is both **physical** (eg: skin, intestinal mucosa, etc. as protective barriers) and **chemical** (acidity of the stomach). The body responds with an inflammatory response, which sends blood to infected sites and allows white blood cells (neutrophils, monocytes, macrophages) to engulf the pathogen through phagocytosis, and destroy it with enzymes. NKCs ("natural killer cells") are also part of the immune defense system by detecting abnormal cells and eliminating them. As for dendritic cells, they relay information from the innate immune system to the acquired immune system.



• The adaptive / acquired immune system: unlike the innate system which is non-specific, the acquired system uses information about the invading pathogen to develop a dedicated, stronger response with immunological memory. There are 2 types: humoral antibody-mediated immunity (by B cells), or cell-mediated immunity (by T cells), both of which can be supported by optimized nutrient intake.



#### Fig. 1 : Diagram of the innate and adaptive immune system

### **KEY NUTRIENTS OF THE IMMUNE SYSTEM**

Public health practices such as hygiene measures (hand washing) and vaccinations help reduce the impact of infections. However, sometimes certain additional measures are necessary to support individual immune systems. The role of nutrition in supporting the immune system is known and established.

Certain micronutrients demonstrate support for immune defense. It's the case of :

- vitamins (A, B6, B12, C, D and E)
- **trace elements** (zinc, copper, selenium, iron, magnesium)
- omega-3
- and beta glucans (polysaccharides)

which participate in the proper functioning of innate and adaptive immunity. A deficiency or under-intake of these micronutrients has a negative impact on resistance to infections. In addition, the **antioxidant nutrients** (vitamins C and E, selenium, copper and zinc):

- act against damages caused by reactive oxygen species (= ROS, including free radicals, superoxides) to cell tissues
- moderate immune function through their effect on the production of cytokines and prostaglandins, as well as on the regulation of transcription factors sensitive to redox potential.

We will particularly focus on the role of minerals in the immune response: first of all **zinc** and **copper** for their direct action in the biological processes of **immunity**, then **magnesium** in its help to **fight against stress** (responsible for weakened immune system) and its **role in the vitamin D synthesis**.



### BENEFITS OF MINERALS AND TRACE ELEMENTS FOR THE IMMUNE SYSTEM

## ZINC, a key element of the immune response

Zinc is the most abundant trace element in human metabolism after iron, with a total estimated amount of between 2 and 4g. The greatest concentration of this trace element is found in muscle, bone, skin and liver.

It has a predominant role in many metabolic and chronic pathologies: diabetes, cancers, neurodegenerative diseases. There is also a strong correlation between zinc deficiency and infectious diseases such as malaria, HIV, tuberculosis, measles and pneumonia.

### *Zinc is present in the functioning of more than:*

- 2000 metalloproteins and metalloenzymes, that is to say proteins or enzymes which have a metal as a cofactor and which cannot function without (zinc, but also copper, manganese, etc.).
   Zinc is for example cofactor of thymulin, hormone of the thymus involved in the maturation of T lymphocytes.
- 750 «zinc-finger» transcription factors allowing the transcription of genes, the synthesis of DNA and RNA

The human body **does not have a zinc reserve and storage system** (unlike iron), it is important that a daily intake is made.

Zinc has many functions, and is essential for everyone. It promotes healthy skin and hair, improves blood sugar regulation, is necessary for cell growth (RNA and DNA replication), brain functions, reproductive functions, thyroid function, vision (day and night), blood coagulation, mood modulation, and above all, in the efficiency of the immune response.

Mild zinc deficiencies are very common, especially in our modern society in which the heavy use of pesticides and intensive farming / animal husbandry has decreased the mineral content of food. It is estimated **that 20-30% of the world's population is deficient in zinc.** 

Certain categories of the population are more deficient in zinc than others, including:

- vegetarians (because in foods zinc is found more in meat and seafood)
- patients with hepatitis or HIV (by the way zinc is recommended in combination with antiretrovirals)
- liver and intestinal patients
- the elderly (drug interactions, alterations in intestinal functions, etc.)

External factors can also decrease the absorption of zinc:

- A diet rich in vegetables and cereals, containing phytates which decrease its absorption
- Alcohol consumption (increased excretion, effect on the liver)
- Consumption of diuretics
- Consumption of calcium channel blockers (for hypertension, heart problems)

A zinc deficiency results in extremely varied and unspecific symptoms, which means that it is not always easily identified: fatigue, infections, skin problems, loss of hair, taste and smell, problems fertility, vision, etc. etc. In the case of significant deficiencies, the consequences are serious: defective immune system, thymic atrophy ...

As Linus Pauling said (Nobel price of medecine):

"You can trace every sickness, every disease and every ailment to a mineral deficiency." Linus Pauling

Zinc is, and has been proven by numerous studies, **a modulator of the immune response**.

It thus has 2 functions in this area:

- Zinc enhances immunity by activating B and T lymphocytes (especially as a thymulin co-factor)
- It **prevents viral replication** and therefore the intensity and duration of the symptoms of the infection

We also note, and this is particularly important in the context of a global Covid-19 pandemic: **zinc regulates proinflammatory cytokines**, and can therefore be of effective support to limit what is called the **cytokine storm** characteristic of Covid-19, and fatal to humans.

Zinc is also a **co-factor of SOD** (superoxide dismutase), a metalloprotein essential component of the **elimination of free radicals**, and therefore beneficial for the defense against oxidative stress. Finally, zinc in its contribution for maintaining the **integrity of the skin and mucous membranes** (the first physical barrier against infections) participates in the innate immune defense.

Zinc deficiency results in:

- Increased oxidative stress
- A weakened formation, activation and maturation of lymphocytes
- Inter-cell communication via cytokines disrupted
- Weakened innate host immunity



#### Specific additionnal interest in Covid-19 treatment: influence of zinc on the loss of taste and smell

In addition to its benefits for the immune system, zinc has an interesting effect that is specific to one of the consequences of Covid-19: loss of taste (dysgeusia or even ageusia) and smell (anosmia). A 2005 clinical study with a strong zinc gluconate treatment (140mg / day) on 50 patients against placebo demonstrated a very strong reduction in the problem of dysgeusia. The treatment also alleviated the depressive symptoms in patients treated with zinc gluconate.

## Zinc rich foods and recommended intakes

The main cause of zinc deficiency is malnutrition, in the sense of a deficiency in nutrition but also imbalances in a person's nutritional intake. Foods of animal origin are the richest in zinc and in particular: seafood (oysters, crabs, lobster, lobster) and meats (veal, beef). Nuts and grains also, but with the disadvantage of also being a source of phytates which decrease its bioavailability. This makes it more difficult for vegetarians or vegans to meet zinc requirements.

However, it is important to note that the zinc in food is not fully absorbed by the human body. It is estimated that 15 to 40% of the zinc in food is actually absorbed. Adults have a recommended daily zinc intake of 8 to 11mg, and slightly more for pregnant women (11-13mg). In a situation of increased risk of infection, zinc supplementation can be useful both to strengthen immunity or to inhibit the replication of a virus already present. In the phases where the risk of infection is increased, we recommend between **15 and 30 mg** of intakes per day.

#### How to chose the best form of zinc

The effectiveness of a zinc dietary supplement depends largely on the chemical form in which the zinc is present. Indeed, the zinc salt must be soluble and coupled to an organic vector that the human metabolism will be able to recognize and assimilate.

For example, **inorganic forms** of zinc (oxide or sulphate) will contain a high proportion of zinc, but since these forms are not or hardly soluble and these vectors are not biomimetic, the mineral salt will not be assimilated but excreted by the body. Their bioavailability is low, and they will have a negative effect on the gastron-intestinal tract.

On the other hand, **organic forms** having slightly lower zinc contents but a vector allowing passage through the gastrointestinal tract until complete absorption, are for their part perfectly recognized and bioavailable.





There are also other organic amino forms such as bisglycinates, but often coupled with additives (masking the taste, artificially increasing the mineral content ...), having poor solubility. Bioavailability is also a concern, as the mineral is coupled to 2 glycine molecules giving it a cyclic and rigid conformation which does not facilitate the release of the mineral once it has reached the final site of absorption. It should be noted that the bioavailability of zinc will also depend on the diet. Indeed, certain components present in plants (phytates, lignin), certain fibers, will inhibit the absorption of zinc.

### **BENEFITS OF MINERALS AND TRACE ELEMENTS FOR THE IMMUNE SYSTEM**



#### Like zinc, copper is a trace element that catalyzes reactions involved in the immune response process, as well as a good antioxidant.

Its usefulness was understood relatively late, notably thanks to a 1964 study of Peruvian children with malnutrition, who showed severe anemia, neutropenia (low levels of neutrophils in the blood) and bone malformations, but responding positively to copper supplementation. Since then, a huge amount of research has attempted to explain how copper works in human metabolism. To date, it has been shown that copper plays a role of co-factor of metal enzymes such as super-oxide dismutase (SOD, involved in the fight against free radicals) and cytochrome-c-oxidase (involved in electron transport).

Copper is necessary for metabolism, in smaller quantities than zinc: an intake of **1** to **3 mg/day** is sufficient. As with zinc as well, Westerners are mostly deficient, which leads to a decline in immunity.

Copper is important for both innate and acquired immunity:

• The **level of neutrophils** (white blood cells of the immune response arising in the bone marrow) is reduced in the event of copper deficiency, as well as their ability to generate superoxide anions and destroy ingested microorganisms, even in the event of a deficiency minimal (this is neutropenia). It is also believed that phagocytes released during the innate immune response use concentrations of copper to kill bacteria, and work to prevent the pathogen from acquiring copper. Studies have shown high copper concentrations as close as possible to infection sites.

 In addition, recent research has shown a link between the reduced presence of interleukin-2 in copper deficiency, which induces a reduction in the proliferation of T lymphocytes, responsible for acquired cellular immunity.



## Direct bactericides functions of zinc and copper

We have seen that copper and zinc play a determining role in the overall mechanism of immune function (innate and acquired). However, since 2015, studies show that these minerals also have a **direct function on the survival of pathogens** that have attacked the host.

This is an extremely recent line of research, and the mechanisms are not yet clearly identified for copper. Nevertheless, the hypothesis retained is that the phagocytes would directly capture the available free copper and use it as its **own antibacterial agent** which would be toxic for the survival of the pathogen in the host organism.

The mechanism of zinc is easier to understand since it acts on the DNA replication of pathogens. Zinc's nutritional immunity is also exemplified by the action of calprotectin, which sequesters zinc and manganese and deprives the pathogenic bacteria of this trace nutrient.

# **Copper rich foods and how to chose the best forms of copper supplement**

In the same way as for zinc, the organic forms are to be privileged (compared to inorganics such as: copper oxide, copper sulphate), and in particular copper gluconate, bioavailable, well tolerated and well documented. The recommended dose of copper is **1.5 to 3 mg/day**.

Iron and zinc are antagonists to copper, and decrease its absorption. Therefore they **should not be taken at the same time**. It is also recommended to take breaks between zinc supplementation cures.

In food, copper is found in : nuts, seeds, liver and kidneys, bran, wheat germ, pulses, seafood and shellfish.



BENEFITS OF MINERALS AND TRACE ELEMENTS FOR THE IMMUNE

#### Magnesium : stress reducer and vitamin D precursor

#### Biological researchers have suspected a link between stress and weakened immune defenses for several years, but the mechanism remained unknown until then.

This was confirmed in 2020 with a study by INSERM which demonstrated an effect of stress on  $\beta$ -2 adrenergic receptors, the stimulation of which reduces the immune response (by paralyzing cytokines). Stress also decreases the capacity for recovery by monopolizing part of the immune system.

Stress affects a number of metabolic processes (heart rate, breathing, muscle contraction, etc.) but we now know that it also activates the production of active white blood cells that can damage healthy tissue. It also damages the intestinal wall which becomes the site of inflammatory reactions, decreasing the absorption of nutrients necessary for the proper functioning of the human body.

In fact, in the acute phase, stress releases a high concentration of catecholamines, which leads to a loss of intracellular magnesium. The resulting magnesium deficiency will in turn increase sensitivity and vulnerability to stress and the vicious circle is set in motion.

In 2017, an English review listed 18 clinical studies on magnesium supplementation as part of the management of stress. These studies report positive effects of magnesium against a placebo, but also some report an equivalent efficacy of magnesium against anxiolytics. A french study in 2016 also demonstrates the benefits of a combination of magnesium, vitamines and probiotics on stress, which effects up to one month after the end of the treatment.

Magnesium salt	content	(g/L, at 20°C)
Magnesium glycerophosphate - GIVOMAG ®	12,5%	80
Magnesium gluconate	5,90%	110
Magnesium citrate	11,90%	0,6
Magnesium lactate - GIVOBIO La/Mg ®	10,20%	80
Magnesium bisglycinate	11,60%	10
Magnesium aspartate	7,50%	1000
Magnesium pidolate	8,70%	50

## Magnesium, vitamin D and COVID-19

Nutrients usually act in a coordinated manner in the body. Intestinal absorption and metabolism of a given nutrient depends on the availability of other nutrients. For instance, magnesium assists in the activation of **vitamin D**, a vitamin having a protective effect against respiratory tract infection and attenuate various proinflammatory cytokines mediating the incontrolled cytokines storm leading to severe forms of COVID-19. All the enzymes that metabolize vitamin D seems to require magnesium. In return, vitamin D can increase magnesium (and phosphate) absorption in the intestine. Vitamin D3 (cholecalciferol) is produced in the skin when exposed to sunlight, thus is not a « real » vitamin. Vitamin D2 (ergicalciferol) has a vegetal origin.

Since modern life does not offers diets containing enough vitamin D, nor enough safe sunlight exposure, supplementation of Vitamin D is necessary to avoid deficiency. However, neither D3 or D2 have enough bioalogical activity by themselves : this is where magnesium can help and its positive influence on vitamin D activity has been proven by clinical studies.

Last but not least, in June 2020, a clinical study realised on COVID-19 patients hospitalized in Singapore demonstrated the benefits of a combination of **Vitamin D3**, **magnesium** (150mg/day) and **vitamin B12**. It resulted in a significant reduction in the proportion of patients with clinical deterioration requiring oxygen. This particular combination of vitamins and magnesium was chosen because of the ingredients direct role in tempering the inflammatory response to viral infections.

# Magnesium rich food and how to chose the best magnesium form of supplement

The dietary sources of magnesium are: chocolate, nuts, dried fruits, green vegetables, fish and seafood. With once again the downside of the presence of phytates in foods of plant origin which bind to mineral and prevent its absorption.

As with all minerals, not all forms of magnesium are created equally.

 The first generation of magnesium salts, known since Antiquity, is made up of inorganics salts: oxides, chlorides and sulphates (sometimes appearing as «marine magnesium» or «mother liquors»), magnesium carbonates. They have a very low bioavailability (poorly soluble and carriers of magnesium not «biomimetic»), a laxative effect, cause abdominal pain, gas and disturb the acid-base balance. In the case of acute or chronic stress, we have seen that stress is already a factor of accelerated transit and malabsorption, a risk of additional diarrhea should therefore be avoided.

- The **second generation** combines magnesium with **organic vectors**, such as: gluconate, lactate or magnesium citrate, which are soluble forms recognized by the body.
- Finally, the **third generation** consists mainly of magnesium glycerophosphate, a non-laxative and highly bioavailable salt. Magnesium bisglycinate is also part of this generation of premium minerals, with the drawbacks previously mentioned for zinc (low solubility, presence of additives, difficult release of the mineral linked to the rigid structure of the molecule)

Magnesium salts are sometimes combined with vitamins (especially B6 and D, which facilitate its absorption) and selenium. Fermentable fibers (prebiotics) promote absorption as well, and magnesium gycerophosphate in particular is very **compatible with probiotics**.



## CONCLUSION

It is necessary to **maintain an effective immune system** throughout life, and even more so in a modern environment comprising a variety of factors which have a bad influence on this balance (foods less rich in nutrients, pollution, stress, malnutrition). Nutrient deficiencies have been shown to be present all over the world. A healthy lifestyle is preferred, and must take into account the intake of a variety of nutrients in the optimal amounts for the proper functioning of the metabolism. **Ensuring your intake of vitamins and minerals** is already an insurance of well-being and health. In particular, a diet or supplementation rich in: vitamins A, B6, B12, C, D and E and in trace elements such as zinc, copper, selenium and magnesium helps protect the metabolism against infections and various diseases. Finally, we now know that the gut and immunity are closely linked, and that the role of prebiotics and probiotics will also be at the forefront in this area.

This document is based on scientific publications and technical information available at the time we wrote it. The information indicated in this document are for information purpose and given as a guide within the scope of our technical assistance commitment. ISALTIS cares to ensure that the information provided in this document are correct and accurate. However, we do not engage ourselves on the completeness of the information, neither on the legal claims related to the cited ingredients, which may vary upon countries/region. Please consult your local regulatory professional for legal advice.

#### REFERENCES

1. **Increasingly proactive consumers**. Actif's magazine n°71, 2020 p.38-41

2. **The Role of Zinc in Antiviral Immunity,** Scott A Read,1,2 Stephanie Obeid,3 Chantelle Ahlenstiel,3 and Golo Ahlenstiel1,2. American Society for Nutrition 2019.

 Zinc and its role in immunity and inflammation, Paola Bonaventura, Giulia Benedetti, Francis Albarède, Pierre Miossec, Autoimmun Rev. 2015 Apr;14(4):277-85

4. Zinc in infection and inflammation, Gammoh NZ., Rink L., Nutrients 2017, 9, 624

5. **Zinc and immunity : an essential interrelation**. Maares M., Haase H., Arch. Biochem. Biophys. 2016, 611, 58-65

6. The key role of zinc in elderly immunity: A possible approach in the COVID-19 crisis, Poliana Guiomar de Almeida Brasiel . Clinical Nutrition ESPEN 2020 Aug;38:65-66.

7. The efficacy of zinc supplementation in young children with acute lower respiratory infections : a randomized double-blind controlled trial. Shah UH., Abu Shaheen AK., Malik MA., Alam S., Riaz M., Al Tannir MA. Clinical Nutrition, 2013, 32, 193-199

8. Zinc and Regulation of Inflammatory Cytokines: Implications for Cardiometabolic Disease. M. Foster, S. Samman. Nutrients. 2012 Jul; 4(7): 676–694.

 Effects of zinc supplementation in the prevention of respiratory tract infections and diarrheal disease in Colombian children: A 12-month randomised controlled trial. N.S.Martinez Estevez, A.N.Alvarez-Guevara C.E.Rodriguez-Martinez. Allergol. Immunopathol. 2016, 44, 368-375

10. Contribution of selected vitamins and trace elements to immune function. E.S.Wintergerst, S.Maggini, D.H.Hornig. Ann. Nutr. Metab. 2007 ; 51 :301-323

11. **Zinc gluconate in the treatment of dysgeusia, a randomized clinical trial.** S M Heckmann 1, P Hujoel, S Habiger, W Friess, M Wichmann, J G Heckmann, T Hummel. J Dent Res 2005 Jan;84(1):35-8 doi: 10.1177/154405910508400105

12. **Copper and immunity**. S.S. Percival. Am. J Clinical Nutrition, 1998 ;67(suppl) :1064S-8S  The role of Copper and Zinc toxicity in innate immune defense against bacterial pathogen. K.Y.Djoko, C-L Y.Ong,
 M.Walker, A.G.McEwan. Journal of biological chemistry, Vol. 290, No 31, p18954-18961, July 31, 2015

14. The immune system as a physiological indicator of marginal copper status. M.Bonham, J.M.O'Connor,B.Hannigan, J.J.Strain. British Journal of Nutrition (2002), 87, 393-403

15. INSERM communication of March 2020 : **Quand le stress** affaiblit les défenses immunitaires

16. **Therapeutic options for the treatment of 2019-novel coronavirus: An evidence-based approach** Phulen Sarma, Manisha Prajapat, Pramod Avti,1 Hardeep Kaur, Subodh Kumar, and Bikash Medhi Indian J Pharmacol. 2020 Jan-Feb; 52(1): 1–5.

17. Micronutrients and ageing: intakes and requirements, M J Richard 1, A M Roussel. Proceedings of the Nutrition Society 1999 Aug;58(3):573-8

 Thesis : « Le magnésium dans la prise en charge du stress à l'officine », Magali Avensac, Université Toulouse III Paul Sabatier, 2018, 2018/TOU3/2039

19. **Exercise, magnesium and immune function,** M.J.Laires, C.Monteiro. Magnesium research 2008 ; 21(2) :92-6

20. Optimal nutritional status for a well-functionning immune system is an important factor to protect against viral infections, P.Calder, A.Carr, A.Gombart, M.Eggersdorfer, Nutrients 2020, 12, 1181 ; doi :10.3390/nu12041181

21. Role of magnesium in Vitamin D activation and function. A-M Uwitonze, M.S. Razzaque. The Journal of the american ostheopathic association. March 2018, Vol. 118, N°3.

22. Cohort study to evaluate effect of Vitamin D, magnesium and vitamin B12 in combination on severe outcome progression in older patients with coronavirus (COVID-19). Chen Wen Tan and al. Singapore General Hospital. Nutrition doi: 10.1016/j.nut.2020.111017

23. **EUROPEAN DIRECTIVE 2008/100/CE** of comission on October 28th 2008

24. **EFSA Claims** - EU Register of nutrition and health claims made on foods

#### About us – ISALTIS, a key partner for minerals

ISALTIS is a French company with an international scope, which designs and develops organic mineral salts at its two sites in Lyon and Thénioux (18), using processes that respect the environment and the principles of Green Chemistry. ISALTIS is a company driven by science and active in nutrition, pharma, cosmetics and veterinary. We offer high quality ingredients, of natural origin and proven to work; as well as contract premixes and scientific support in the fields of the health of the world population.

ISALTIS offers mineral salts:

- Without additives
- 100% Vegan
- Without pesticides
- GMO free
- Made in France

ISALTIS and its mother company MACCO ORGANIQUES are the leading the domain of minerals for Life Sciences. They both belong to LALLEMAND group, specialised in the development and production of yeasts and bacteria.

For more information on our ability to support you in the development of effective and innovative nutritional solutions, visit our website: www.isaltis.com

### ISALTIS

ISALTIS – site Givaudan-Lavirotte 56 rue Paul Cazeneuve 69008 LYON, FRANCE +33 (0)4 78 61 55 00 contact@isaltis.com www.isaltis.com