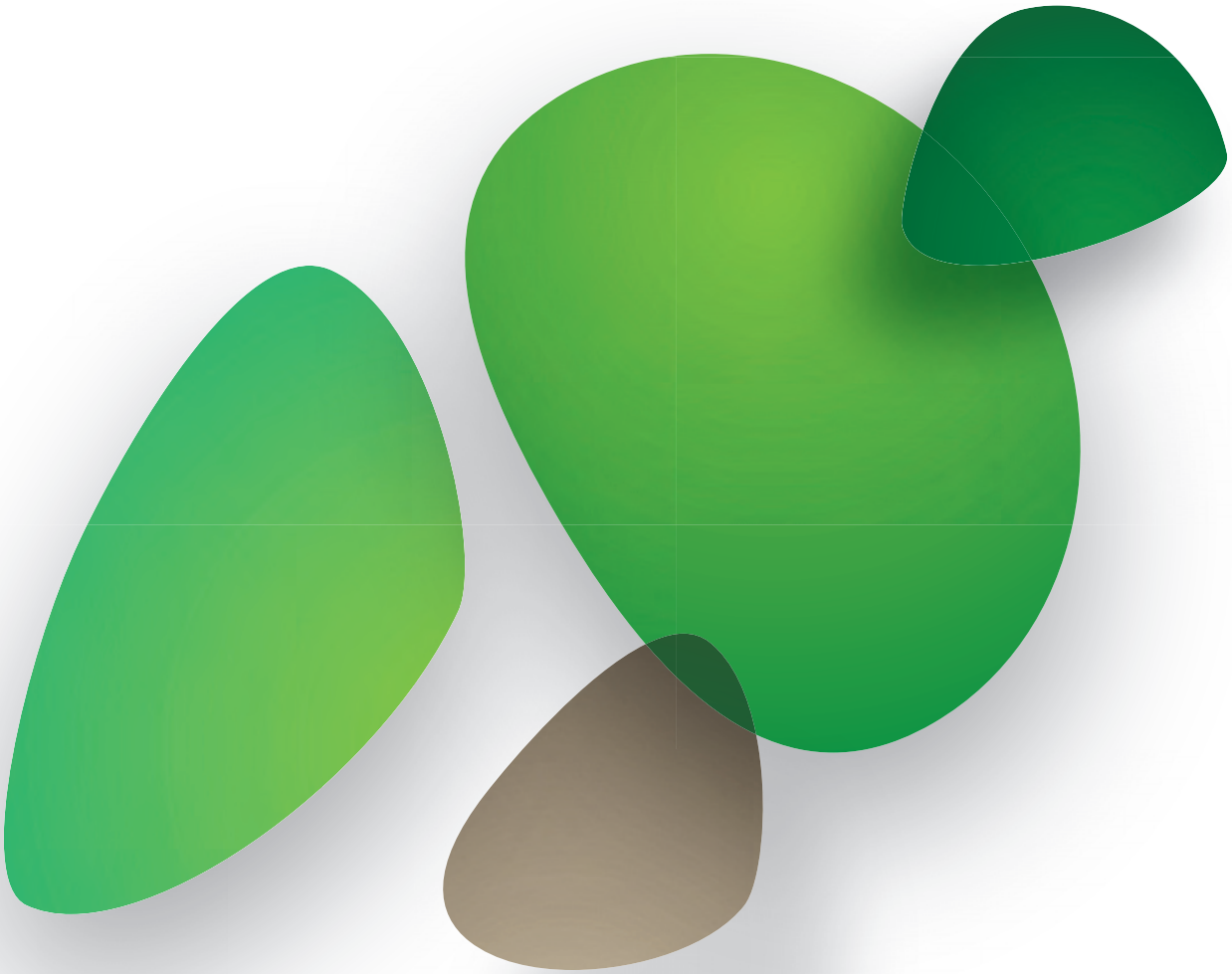
Quatrefolic®

The innovACTIVE folate!

White PAPER

Gnosis by Lesaffre



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Introduction

A growing amount of data indicates that a series of nutrients, bioactive dietary components and changes in diet habits could modulate the patterns upon a series of organs, systems and vital functions that as a whole determine the health status of people at all the stages of life.

Since the beginning of its activities in 1989, Gnosis by Lesaffre has been committed to improving the quality of life of humans promoting their well-being by supplying innovative solutions and ingredients of natural origin with scientifically proven efficacy when are consumed throughout lifetime as a part of the daily diet.

Innovative global player in yeast, bacteria and pure molecule from fermentation, Gnosis by Lesaffre provides scientifically-proven and sustainably-sourced active ingredients and solutions to customers in the pharmaceutical, nutritional and functional food industries for a wide range of health benefits.

Quatrefolic®, the innovActive folate is the biologically active form of folate everyone can immediately utilize without any kind of metabolization, one of the most impressive results of the capacity of Gnosis by Lesaffre to merge excellence in biotech innovation and constant evolution in nutraceutical applications.

Quatrefolic® is also an evidence of how Gnosis by Lesaffre is leader and really cares about the world of folate, fostering its knowledge, which is a fundamental and key point for a good health.

With this White Paper we are pleased to share with you an informative report on Quatrefolic® and the new research topics of folate application with specific reference to the role of the polymorphism of the enzyme Methylentetrahydrofolate reductase (MTHFR).

Quatrefolic® Network

How to discover daily the many benefits of Quatrefolic® in human health and to be clearly and directly informed?

Follow our social that are updated every day, link with us and discover every news.

Quatrefolic®

The innovACTIVE folate!

Contents

NUTRITIONAL BIOCHEMISTRY OF FOLATE

If the word folate sounds like foliage to you, this is not an accident.

The words share a common root (the Latin word folium, meaning "leaf"), which helps remind us that green plant foods can be among the richest sources of folate. However, as the chart below shows, there are outstanding sources of folate in other food groups as well, especially legumes.

Folic Acid

Folic acid (like food folate) is inactive and needs to be metabolized to 5-methyltetrahydrofolate (5-MTHF) to become metabolically effective.

Total folate content in some common foods

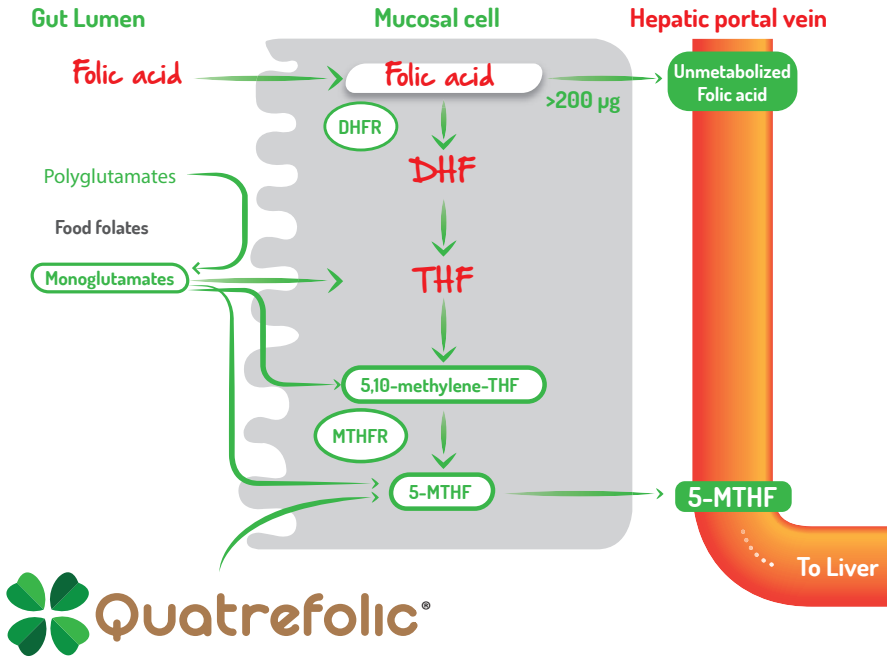
Vegetables	µg/100g	Fruit	µg/100g	Meat	µg/100g
Spinach	150	Chestnuts	62	Beef liver	330
Brussels sprouts	135	Pistachio nuts	58	Pork liver	295
Asparagus (can)	96	Almonds	48	Eggs	50
Broccoli	90	Oranges	3	Ham	19
Herbs (leaves)	89	Almond paste	2	Chicken breast	14
Artichokes	68	Grapefruits	2	Sausages	8

Milk and dietary products	µg/100g	Fish	µg/100g	Other	µg/100g
Camembert	102	Tuna	20	Yeast	1,250
Grana cheese	55	Eel	16	Adzuki beans	622
Gorgonzola	52	Octopus	6	Dried lentils	110
Cheddar cheese	33	Trout (oven)	15	Pasta	34
Yogurt	7	Crustaceans	14	White bread	29
Milk	6	Herrings	11	Rice	20

Typical folate intakes are poor in the diets of many individuals for several reasons. Natural folates are susceptible to oxidation, they rapidly loose activity in foods and are largely destroyed by cooking till 90%. Moreover they have a low and incomplete bioavailability.

Most of folate assumption is coming from **folic acid man-made version in** supplements and added to foods. **Folic acid (like food folate) is inactive and needs to be metabolized to 5-methyltetrahydrofolate (5-MTHF) to become metabolically effective.** Today we know that the folic acid has a complex metabolization and that people assuming folic acid may still be gravely folate deficient because of the big variations in how efficiently folic acid is converted into the bioactive form in different people [1,2].

Food folates are hydrolyzed to the monoglutamate form in the gut prior to absorption by active transport across the intestinal mucosa. Therefore, before entering the bloodstream, the monoglutamate form is reduced to tetrahydrofolate (THF) and converted into methyl forms. On the other hand, folic acid is firstly reduced to Dihydrofolate by the enzyme Dehydrofolate Reductase (DHFR) and then to Tetrahydrofolate. **In humans the gut appears to have a very efficient capacity to convert reduced dietary folates to 5-MTHF but limited ability to reduce folic acid.** As a matter of fact, folic acid reaches the liver in unmetabolized form.

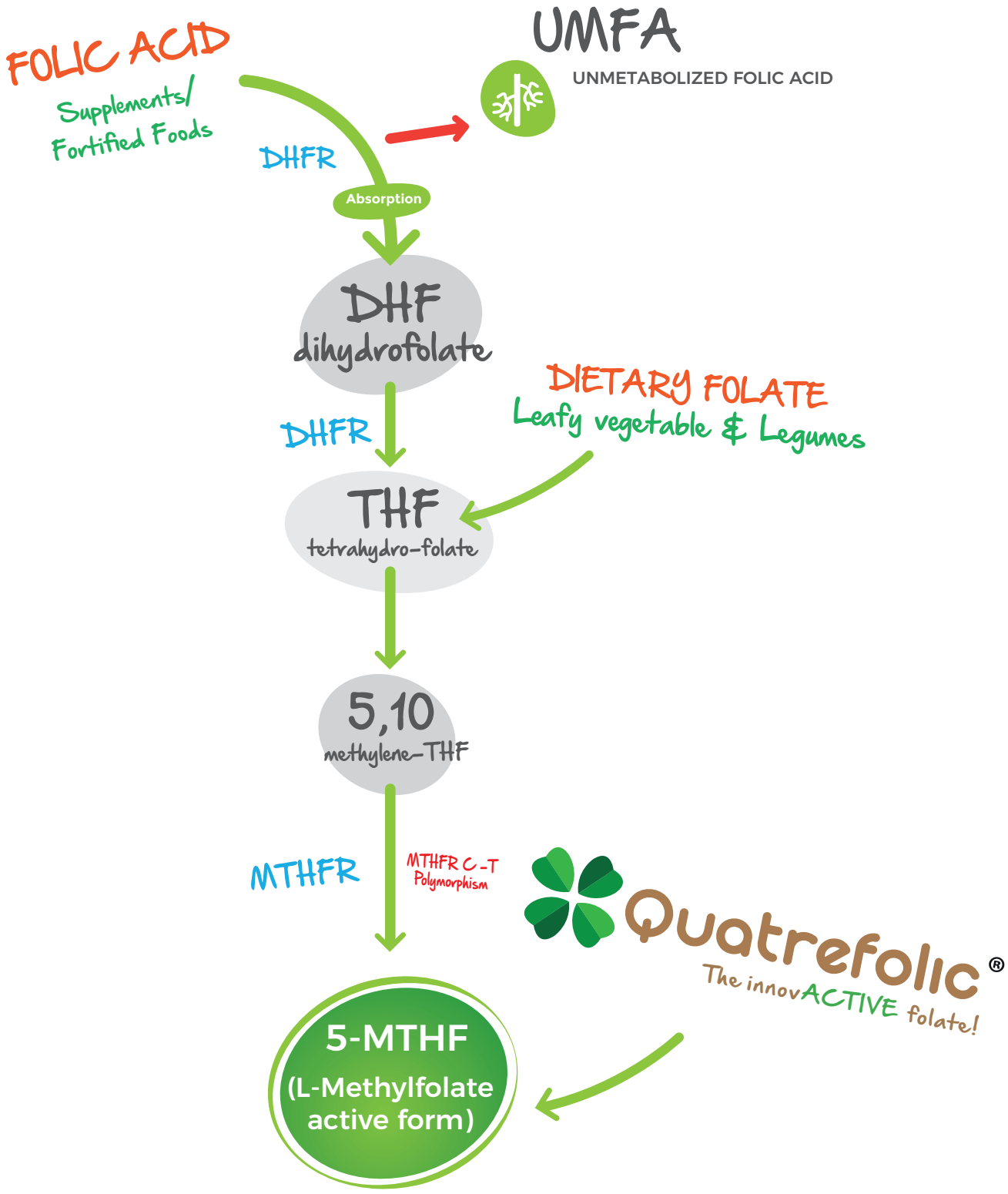


Quatrefolic® passes the gastric barrier and is absorbed mainly in the small intestine by a carrier mediated mechanism. The carrier is not saturated and this enables Quatrefolic® to ensure a higher folate uptake (3,4).

The active form of folate

Quatrefolic® passes the gastric barrier and is absorbed mainly in the small intestine by a carrier mediated mechanism. The carrier is not saturated and this enables Quatrefolic® to ensures a higher folate uptake.

Hepatic biotransformation of folic acid to active folate is critically regulated by two polymorphic enzymes, the DHFR and the MTHFR. DHFR enzyme appears to have low and highly variable activity. Chronic liver exposure to folic acid may induce saturation, which would possibly explain the reported levels of unmetabolized folic acid in the systemic circulation. Additionally, some people have genetic variations that decrease the activity of DHFR. **A study published in 2014 clearly shows that 86% of folic acid in the hepatic portal vein is unmetabolized**, whilst almost all the natural folate was converted correctly (3,4).

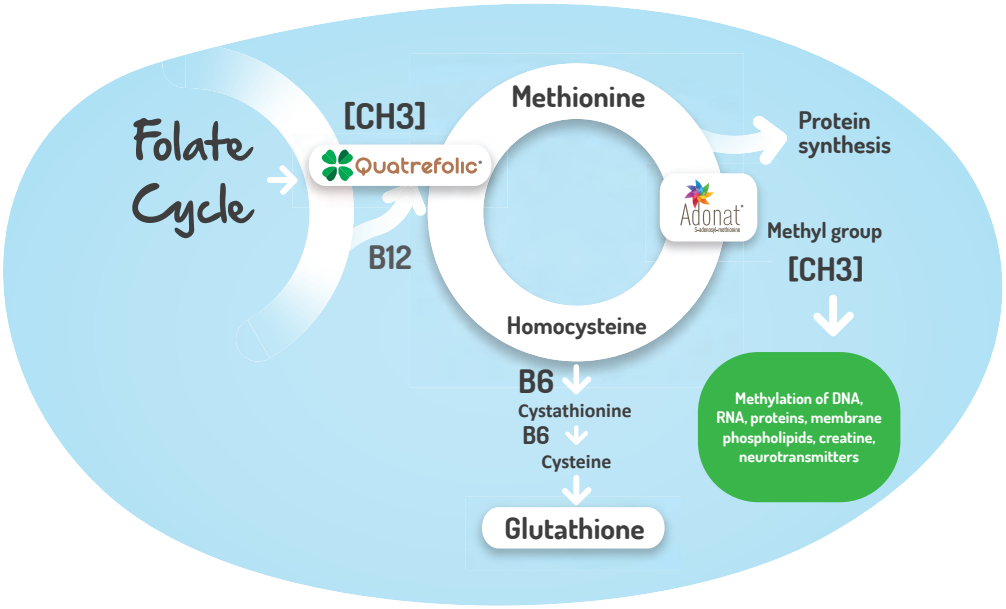


The other enzyme, the Methylentetrahydrofolate Reductase (MTHFR) is also a polymorphic enzyme. Genetic variations, such as the polymorphisms may impair MTHFR activity and the related metabolization of folic acid in 5-MTHF. **MTHFR polymorphisms are estimated to occur in up to 57% of the population** [5,6].

FOLATE AND "ONE CARBON METABOLISM"

Folate-dependent one carbon metabolism and the role of nutritional compounds in regulating biochemical pathways in our bodies are the focus of recent and future investigative research.

Often referred to as the Methylation Cycle, the life critical process is a network of interrelated biochemical reactions that involves the transfer of one carbon methyl groups from one compound to another. **Folate and Methionine are the key components of the Methylation Cycle and are required for normal healthy cellular function** [7,8].



One carbon metabolism occurs in all cells of the body and is crucial for a variety of functions, including DNA synthesis, maintaining and regulating genes, adequate cell division and growth, detoxification, energy production, immune function, brain functioning, mood balancing and inflammation controlling.

Therefore maintaining the balance and levels of folate, vitamin B12 and S-Adenosylmethionine (SAMe - Adonat®) can be critical to support various cellular processes, which influence the development, prevention and treatment of various health issues.

Quatrefolic®, the most bioavailable form of folate, can be the preferred choice for active folate supplementation in synergy with SAMe to support and regulate the methylation cycle.

In the recent years clinical and epidemiological evidence has helped to clarify how nutritional supplements can rectify one carbon cycle activity, restoring normal production of key metabolites and the methylation status, supporting the right gene expression.

One carbon metabolism

Gnosis by Lesaffre is the pioneer in the development of products involved in supporting the Methylation Cycle and one carbon metabolism network.

FOLATE HISTORY

The importance of folate nutritional status in health and wellbeing has been recognized through history for more than 60 years. Today folic acid and folate are often used interchangeably, and many health practitioners will not be able to tell the difference, although "folate" is a family of compounds that counts 4 different generations from those naturally present in foods to the innovative Quatrefolic®.

1st generation - Food folate

Refers to the various tetrahydrofolate derivatives naturally present in foods.

2nd generation - Folic acid

Got its name from folium, the Latin word for leaf, when it was isolated from spinach in 1941. It is a synthetic oxidized molecule, that does not occur in nature but can be utilized by the human body as a precursor to form natural folates that are biologically active.

Folic acid lacks coenzyme activity and must be reduced to the metabolically active form within the cell, through a series of biochemical steps before it can be used by the body's cells in vital metabolic pathways such as DNA production, cell reproduction and homocysteine metabolism.

3rd generation (6S)-5-methyltetrahydrofolate calcium salt

In 1989, Bioresearch S.p.A. was the first company to evaluate the real importance of 5-methyltetrahydrofolate and to boost the development and the launch of this innovative natural endogenous compound in the form of stable pharmaceutical composition of calcium 5-methyltetrahydrofolate, being well aware that biological molecules face less risks of adverse effects in humans compared to xenobiotics.

The calcium salt of 5-methyltetrahydrofolate is commercially available and represents the third generation of folate. Before Quatrefolic®, 5-methyltetrahydrofolate calcium salt was the only folic acid derivative available on the market and able to penetrate the body cells without needing further metabolism.

The 4th generation: Quatrefolic®

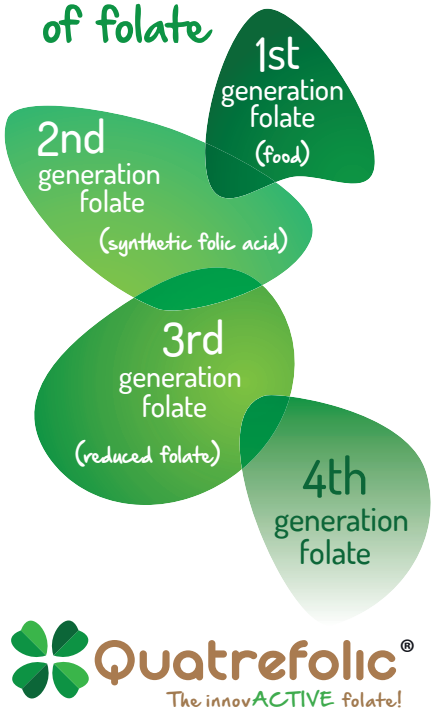
The goal for Gnosis' R&D was to develop an innovative folate salt form able to overcome the existing calcium salt form limitations related to stability and poor solubility. In February 2008, Gnosis patented a new generation of folate derivative, brand named Quatrefolic®, (6S)-5-methyltetrahydrofolate glucosamine salt.

Quatrefolic® represents the fourth generation folate endowed with long lasting stability as well as a peculiarly high water solubility, improved bioavailability and well established safety.

History of Gnosis by Lesaffre

- **1989** Foundation
- **1997** Starting Large Scale Manufacturing
- **2003** Opening of R&D site in Desio (MB)
- **2004** Acquisition of Sant' Antonino (CH) Site from Abbott Knoll Bioresearch (ex Bioresearch S.p.A.)
- **2009** Acquisition of Pisticci Site from Pfizer
- **2011** Opening of Gnosis USA Branch Office
- **2012** Opening of Gnosis China Branch Office
- **2014** US FDA Approval for both Manufacturing Sites
- **2015** US FDA Approval for both Manufacturing Sites
- **2015** Lesaffre majority participation in Gnosis
- **2017** New Warehouse and Advanced Nutrition Plant
- **2018** Full acquisition of Gnosis by Lesaffre

Chronology: The generations of folate



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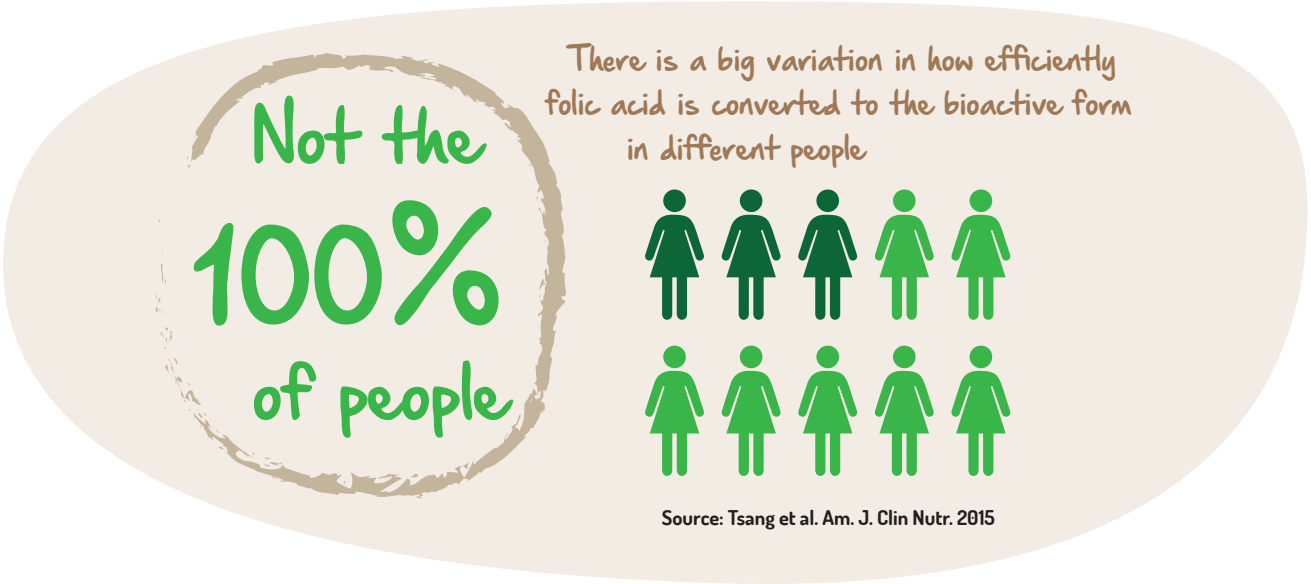
GENETIC POLYMORPHISMS IN FOLATE

In the recent years several evidence of the advantages of reduced folate vs folic acid have been found. **The rational use of reduced folate (particularly reduced and methylated such as Quatrefolic®) is derived from the difficulty of a part of world population to assimilate and metabolize folic acid from food or supplements** [4,9,10].

Folic acid and also food folate are not biologically active and need to be converted to the metabolically active 5-MTHF through a multi-steps process where the enzyme methylenetetrahydrofolate reductase (MTHFR) owns a key role. Some individuals, due to their unique genetic patterns and expression, have polymorphic forms of this enzyme and have an impaired ability to produce adequate or effective amount of MTHFR.



Source: Tsang et al. Am. J. Clin Nutr. 2015

Emerging science of nutrigenomics is shed light how much the MTHFR polymorphism is implicated in chronic disease states and how folate nutrition may contribute to replace adequate methylation and overall health [11].

To date, there are more than 50 known MTHFR variants, but the two prime variants are called C677T and A1298C. The numbers refer to their location on the MTHFR gene. The letters refer to the amino acid position on the MTHFR. The MTHFR is reported as either heterozygous or homozygous [12].

Polymorphic MTHFR enzyme may function approximately 55% to 70% efficiency compared to a normal MTHFR enzyme.

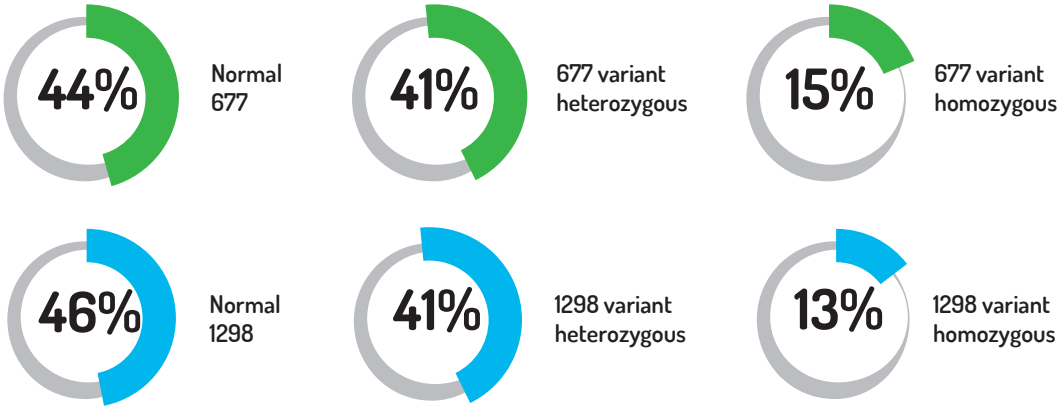
MTHFR variant genes are common!

Genotype	677CC 2 normal 677s	677CT heterozygous one 677 variant	677TT homozygous two 677 variants
1298AA two normal 1298s	100% enzyme activity	66% enzyme activity	25% enzyme activity
1298AC heterozygous one 1298 variant	83% enzyme activity	48% enzyme activity	not analyzed
1298CC homozygous two 1298 variants	61% enzyme activity	not analyzed	not analyzed

The most common MTHFR polymorphism may have a cytosine-to-thymine substitution at nucleotide 677 (677C→T), and an adenine-to-cytosine substitution at nucleotide 1298 (1298A→C), which result in mutations that vary in degree from mild to severe regarding the deficiency of MTHFR enzyme activity [5,13].

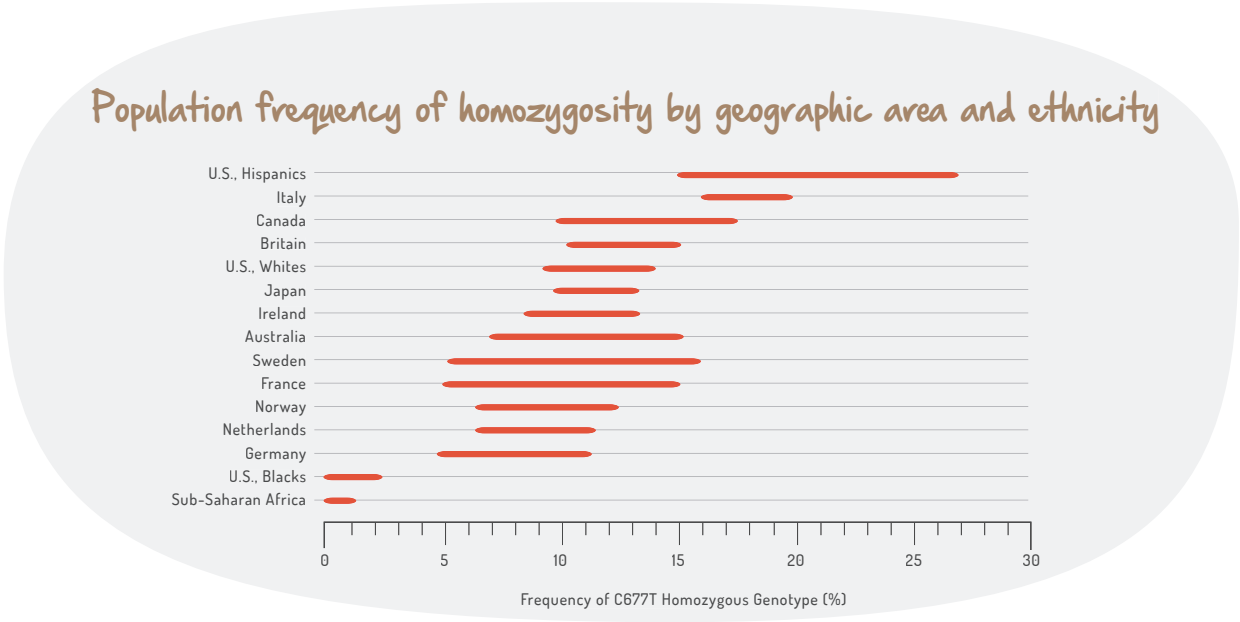
Homozygous means two genes are affected and enzyme efficiency decreases to approximately 7% to 10% when compared to normal. They are also more common among those predisposed to diseases such as cancer, heart disease, and autism, where the mutation frequency can exceed 90% of these populations [10].

Percent of a mixed population containing 677 and 1298 variant genes.



Frequency of the two most common polymorphisms, 677 and 1298 variant genes, found in a mixed population [14].

Current population data shows that MTHFR gene mutations differently affect the world population with gaps especially in some ethnic groups or large geographical areas: higher in the North American Caucasians, Italian and the Hispanics, Mexico (34.8%) and in the North part of China (around 20%) [15,16].



The inability of a part of world population to assimilate and metabolize folic acid from food or supplements may jeopardize their health and increase the risk of adverse health outcomes. The biological active form 5-Methylfolate such as Quatrefolic®, is kindly recommended because efficiently normalize the folate status of all potential subjects including those with MTHFR polymorphism [15].

THE "UMFA", UNMETABOLIZED FOLIC ACID IN SERUM

UMFA

Several studies have reported an increase in serum and unmetabolized folic acid (UMFA) levels since the implementation of folic acid fortification.

Several studies have reported an increase in serum of unmetabolized folic acid (UMFA) levels since the implementation of folic acid fortification, with possible concern about its potential 'overdosing' and adverse effects.

Variability in the presence or persistence of UMFA in the population suggests that it may be accumulated in the blood as a consequence of different conditions described above, such as the impairment, and/or the slackness of the folic acid reduction pathway to the 5-methyltetrahydrofolate (genetic polymorphism), and the overdosing effect due to uncontrolled folic acid intake.

The threshold of ingestion of folic acid that leads to the direct appearance of UMFA in the plasma, results to be highest than 200-300 µg/daily intake. **The consumption of highest dosage of synthetic folic acid results in absorption of unreduced folic acid, which may interfere with folate metabolism for a period of years** [17].

Prevalence of detectable circulating unmetabolized folic acid by quintile category of estimated folic acid intake (18).

The large amount of UMFA in the portal vein is probably attributable to an extremely limited capacity of the enzyme dihydrofolate reductase (DHFR) present in the mucosal cell of the intestine, that is responsible for the first step of reduction of synthetic folic acid to 5-MTHF.

Folic Acid

Synthetic Substance found in supplements and fortified foods

→

Folic Acid creates UMFA

(Unmetabolized Folic Acid)
The body can NOT use UMFA.

Therefore, chronic liver exposure to folic acid in humans may induce saturation, which would possibly explain reports of systemic circulation of UMFA.

Recent studies have confirmed that UMFA is associated with a reduction of natural killer cytotoxicity, which reduces the immune system capacity to kill off malignant or pre-malignant cells. Moreover, it accelerates cognitive decline and anemia in the elderly with low levels of vitamin B12.

Quatrefolic® answers to all consumers' and physicians' concerns relating to potential harmful effects of folic acid administration. As Quatrefolic® provides the metabolic reduced folate form utilized and stored in the human body, the (6S)-5-methyltetrahydrofolate, it does not lead to the potential accumulation of UMFA in the blood, which has no biological function and whose effects are not yet known, also due to the potential uncontrolled assumption of folic acid by diet (10,9).

Quatrefolic® and UMFA

Quatrefolic®, the "active form" of folate avoids the potential accumulation of UMFA in the blood.

BIOAVAILABILITY & SOLUBILITY

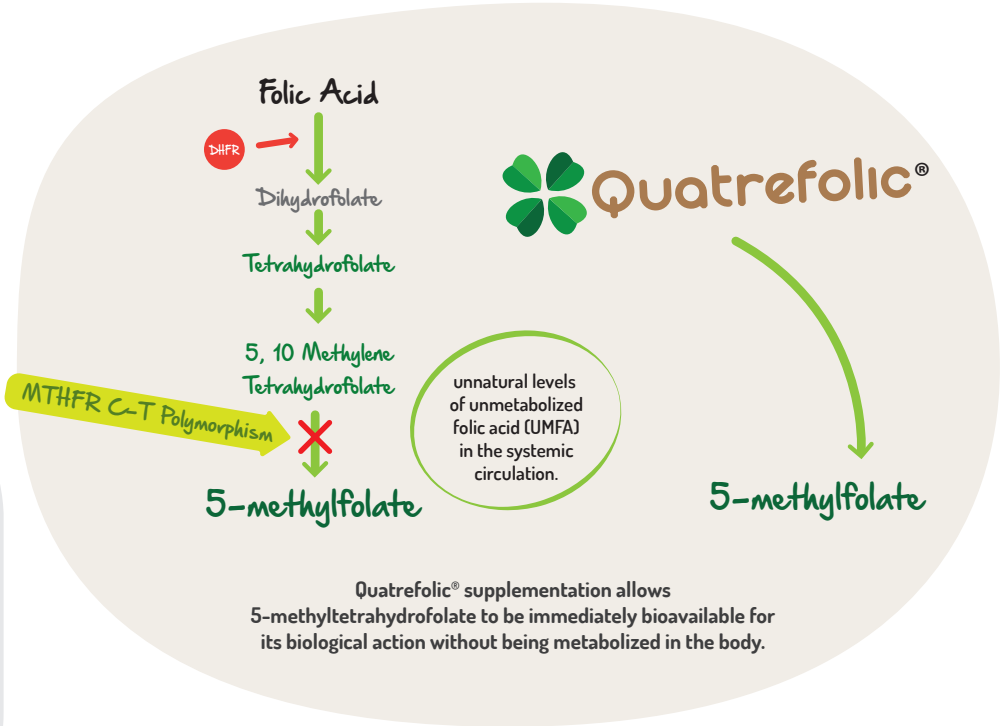
Quatrefolic® is the glucosamine salt of (6S)-5-methyltetrahydrofolate and is structurally analogous to the reduced and active form of folate. Quatrefolic® delivers a "finished" folate the body can immediately use without any kind of metabolization. Choosing Quatrefolic® as a source of folate presents several advantages and solves some problems about folate supplementation:

1) The limited ability of human gut to reduce folic acid to 5-MTHF and related risk that the majority of a physiologic oral dose of folic acid passes into the portal venous circulation in an unmodified form [2,4,19].

2) **The big variations in how efficiently folic acid is converted to the bioactive form in different people due to defect of MTHFR activity** [1,11,20].

3) The inability of folic acid to enter the brain as it is and potential block of 5-MTHF absorption in the brain due to the binding of folate receptors [21,22,23]

4) The low solubility of calcium salt [24].

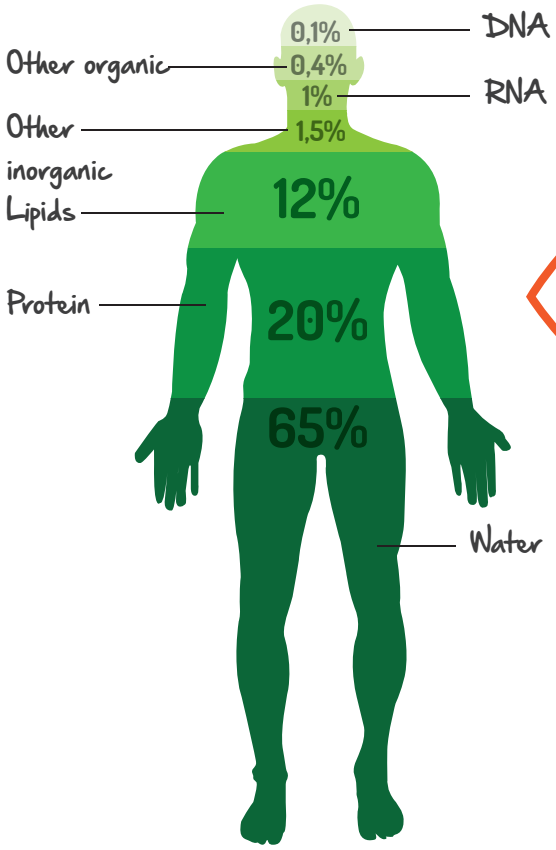


Quatrefolic® is structurally analogous to the active biological form of folate

Quatrefolic® delivers a "finished" folate the body can immediately use without any kind of metabolization.

Quatrefolic® demonstrates a high solubility in water – greater than 1g/1ml – compared to the slight solubility of the competitor compound, (6S)-5-methyltetrahydrofolate calcium salt (1g/100ml), 100 times more soluble.

The oral bioavailability of an active ingredient is highly dependent on its solubility. The absorption of the compound happens after dispersion and solution in gastrointestinal fluid.



The human body is composed of more than 65% of water and any active ingredient to be adsorbed must be present in the form of solution at the site of absorption.

What does solubility mean?

High water solubility means Quatrefolic® may be better absorbed by mucosal cells which may facilitate access to the blood and circulation.

High water solubility means Quatrefolic® may be better absorbed by mucosal cells, which may facilitate access to the blood and circulation with the potential of improving bioavailability.

The extremely higher water solubility of Quatrefolic® is derived from two specific characteristics of the ingredient: the glucosamine salifying agent and the amorphous chemical structure of the product.

The amorphous status provides an intrinsic solubility guaranteeing homogeneous and reproducible solubility process whereas the crystalline alternative cannot.

Glucosamine is a basic, natural, safe and organic salifying agent, chosen after a deep screening operated by Gnosis on more than 100 molecules, as a salt of the biological active form of folate, the (6S)-5-methyltetrahydrofolate, which makes Quatrefolic® 100 times more soluble than the old generation compound, the 5-MTHF calcium salt.

Quatrefolic® is 100 times more soluble in water than calcium salt.

Quatrefolic® solubility

The improved solubility of Quatrefolic® over the (6S)-5-methyltetra-hydrofolate calcium salt represents another advantage achieved by Gnosis in creating a product for applications in the food and beverage industries.

5-methyltetrahydrofolate calcium salt

Quatrefolic®

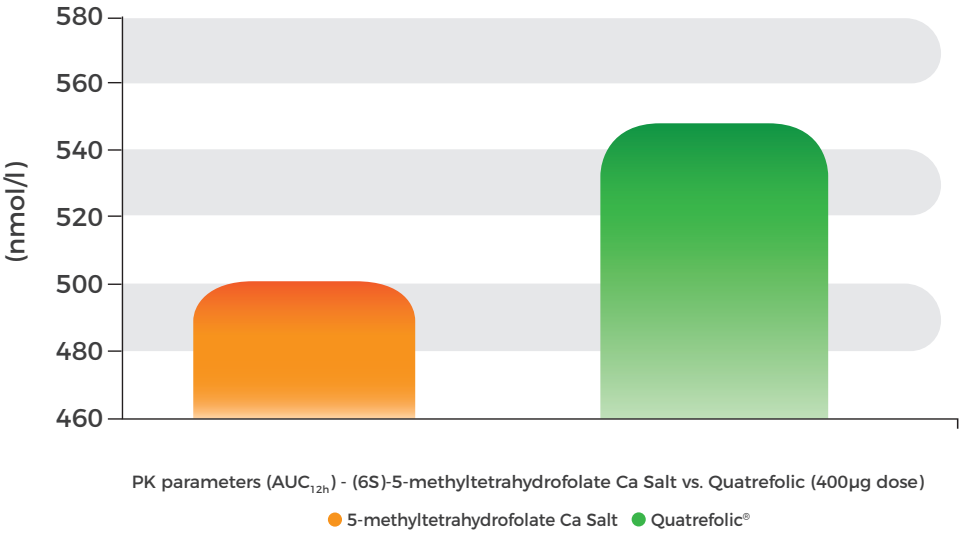
Comparison of solubility in water has been performed evaluating the quantity of solvent needed to solubilize the same amount of each folate derivative, at standard temperature. The improved solubility of Quatrefolic® over the (6S)-5-methyltetrahydrofolate calcium salt represents another advantage achieved by Gnosis in creating a product for applications in the food and beverage industries.

Animal studies and human clinical trial confirm that Quatrefolic® owns a superior bioavailability profile over the (6S)-5-methyltetrahydrofolate calcium salt and folic acid. It was a single dose, balanced, two sequences, two periods, two treatments randomized crossover study [25].

Quatrefolic® and 5-methyltetrahydrofolate: pharmacokinetic comparison

Folic Acid Bioavailability

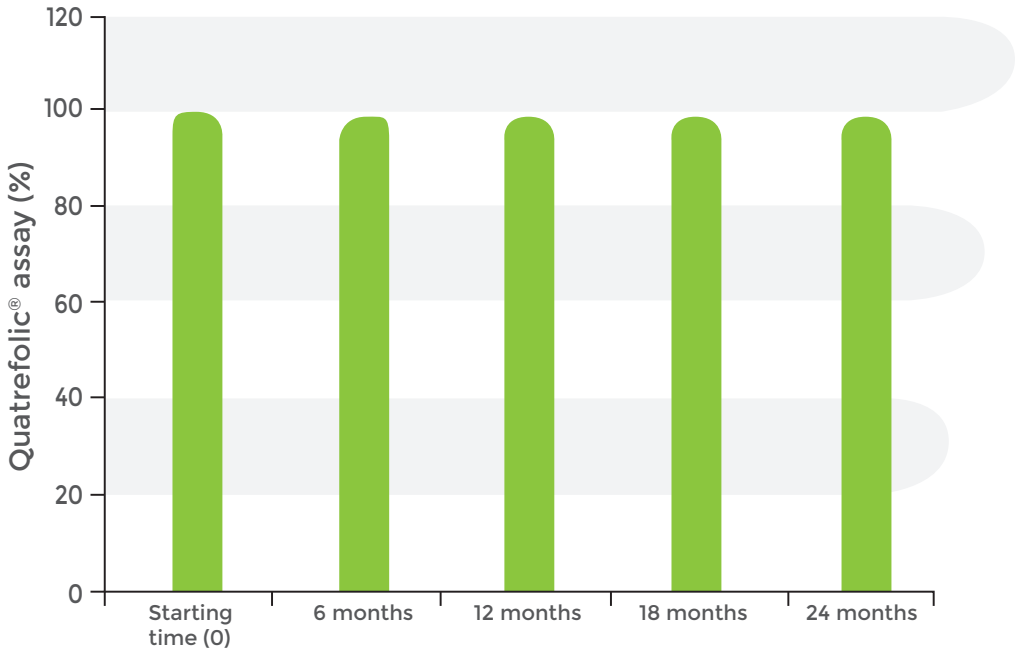
Humans have a limited ability to reduce folic acid to 5-MTHF. The lower bioavailability of folic acid cannot be offset by its increasing intake (2,4,19).



STABILITY

Quatrefolic® shows an extraordinary long lasting chemical stability guaranteeing a quite unaltered purity even after several months, and an assay reduction in 18 months less than 1%, allowing easy handling and storage. The pH of Quatrefolic®, once dissolved, is neutral. This value also provides greater stability to the molecule, protecting it from hydrolytic degradation.

Stability of Quatrefolic® at room temperature



The stability of Quatrefolic® powder form was tested according to ICH (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use) guidelines both at room temperature and other conditions keeping samples in airtight containers, protected from light, and measuring purity and assay at different points.

Gnosis has deliberately chosen to carry out stability tests of Quatrefolic® according to the most strict guidelines, specifically required for pharmaceutical ingredients guaranteeing independent and reliable criteria to claim the long lasting chemical stability to its clients.

The lyophilized ingredient could be handled without specific and restrictive conditions, easily combined with other ingredients and excipients and could be stored at room temperature instead at 2-8°C of the previous folate derivative.

SAFETY

Quatrefolic®, as glucosamine salt of (6S)-5-methyltetrahydrofolate has been the subject of an extensive and relevant number of biological and toxicological studies in order to prove the safety and tolerability of this revolutionary folate. The safe use of Quatrefolic® in pregnancy and lactation has been deeply supported by Gnosis by Lesaffre in the submission of both the New Dietary Ingredient (NDI) Notification at FDA, and the Novel Food at EFSA and the other international submissions [26].

Quatrefolic® is "generally recognized as safe" ("GRAS") for use as a source of folate in conventional and medical foods. The GRAS recognition has been achieved in 2010, by an independent panel of recognized experts - qualified by their scientific and/or medical training and relevant experience – which carried out a critical evaluation of the available data.

The FDA has approved Quatrefolic® as New Dietary Ingredient (NDI) in the same year. The European Novel Food approval has been obtained in 2015. Kosher and Halal Certification have been obtained in 2014.

Quatrefolic® is SAFE

Toxicological tests carried out proved that Quatrefolic® does not induce mutations and it is not cause of chromosomal aberrations.

In 2016, the Australian Therapeutic Goods Administration (TGA) listed Quatrefolic® as permitted ingredient.

In 2017, The Ministry of Food and Drug Safety (MFDS) approves Quatrefolic® as Food Additive in South Korea and The National Health and Family Planning Commission of China officially notified that Quatrefolic® was publicly authorized as Food Nutritional Fortification Substance.

In 2019, Quatrefolic® has been approved by Food Safety and Standards Authority of India (FSSAI) as new food additive to be used as a source of folic acid with the intended health benefits.

Today, several regulatory approvals are in progress in several countries around the world.

Toxicological studies

Gnosis by Lesaffre has performed several in-vitro and in-vivo studies such as mutagenicity, genotoxicity and acute toxicity on Quatrefolic® and the product has met all the safety requirements.

Toxicological tests proved that Quatrefolic® does not induce mutations and it is not cause of chromosomal aberrations. In vivo single dose oral toxicity has been carried out by Gnosis.

Dosage

Quatrefolic® dose is the same of folate, expressed on the basis of the "Recommended Dietary Allowances for Folate for Children and Adults".

As Quatrefolic® provides the metabolic reduced folate form utilized and stored in the human body, it is totally bioavailable.

AGE (years)	MALES AND FEMALES (µg/day)	PREGNANCY (µg/day)	LACTATION (µg/day)
	Folate	Folate	Folate
1 - 3	150	-	-
4 - 8	200	-	-
9 - 13	300	-	-
14 - 18	400	600	500
19 +	400	600	500

Bibliographic reference: Institute of Medicine. Food and Nutrition Board. Dietary Reference Intakes: Thiamin, riboflavin, niacin, vitamin B6, folate, vitamin B12, pantothenic acid, biotin, and choline. National Academy Press. Washington, DC, 1998."

Safety of glucosamine

Glucosamine is a naturally occurring, endogenously produced molecule and thus is not an extraneous compound in terms of the human metabolic process.

Glucosamine is made up of glucose and amino acid glutamine and it is a key building block for several structures.

Several studies show that glucosamine is well tolerated by healthy volunteer subjects at very high dosages, when administered intravenously. Relevant scientific data has been provided related to the effect of glucosamine on sensible categories such as pregnant/lactating women, and children.

The intake of Glucosamine from Quatrefolic® is deemed to be insignificant being equal to 552 µg/day where the acceptable daily intake is 184 mg/kg/day.

Vitamin B12 masking

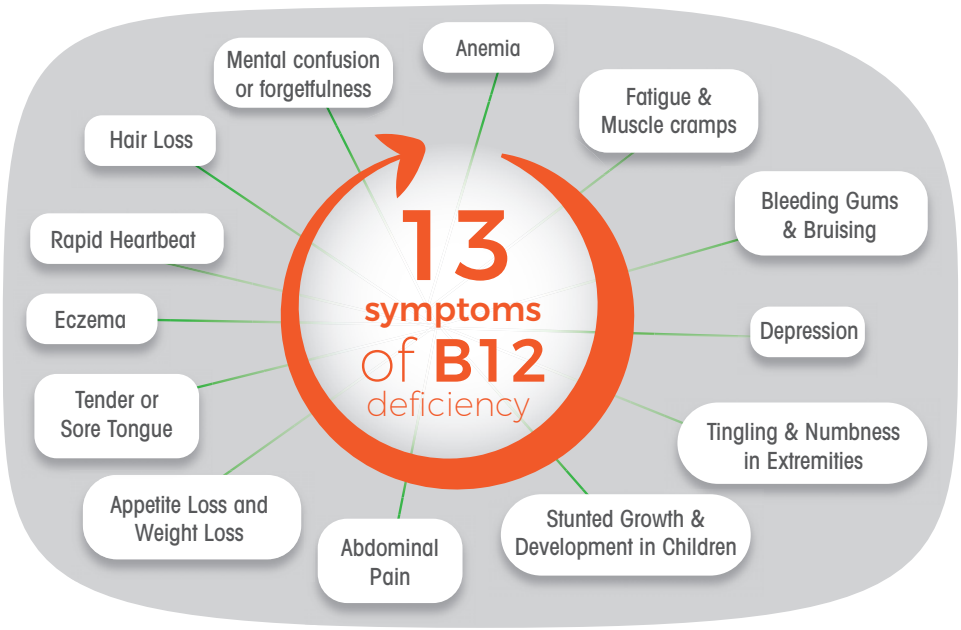
Quatrefolic® is unlikely to mask the vitamin B12 deficiency and its hematologic symptoms as the pathway where it is involved is vitamin B12 dependent.

Vitamin B12 deficiency is common in old age and may not be easy to recognize. People with vitamin B12 deficiency are at risk for nerve damage, anemia and degeneration of the spinal cord. Even relatively mild deficiency can affect brain functions and the nervous system, and the nerve damage may develop into permanent debilitation if left untreated.

People at risk of vitamin B12 deficiency

Vegetarians and vegans, people affected by celiac, autoimmune and Crohn's disease, gastritis, malabsorption syndrome, HIV infection, multiple sclerosis and under specific drug treatment are also at risk.

Folate and vitamin B12 deficiency have the same hematologic symptom, megaloblastic anemia, which disappears after supplementation with large amounts of folic acid (that could be reached thanks to mandatory food fortification with folic acid), particularly in the elderly. Folic acid supplementation may activate synthesis of purine and pyrimidine through a specific pathway correcting anemia, although vitamin B12 is still absent; on the contrary nerve and cognitive deterioration related to vitamin B12 deficiency may continue unchecked.



Quatrefolic®

Quatrefolic® is unlikely to mask the vitamin B12 deficiency and its hematologic symptoms being the pathway where it is involved vitamin B12 dependent.

Quatrefolic® supplementation does not activate purine and pyrimidine synthesis and, if vitamin B12 is absent, 5-MTHF remains "metabolically trapped". This situation produces a "pseudo folate deficiency" because although the cells have adequate levels of folate, it is trapped as 5-MTHF form allowing doctors to diagnostic vitamin B12 deficiency [19,27,28].

QUATREFOLIC® 360° HEALTH

The influence of folate nutritional status has been recognized as critical for human health due to its role in one carbon metabolism, the network of cellular interrelated biochemical reactions involving the transfer of one carbon groups from one biological compound to another (methylation). Folate deficiency has far-reaching negative health consequences at all stages of life. In fact, folate– dependent one carbon transfer is required for DNA synthesis and cell division, regulation of gene expression, amino acid metabolism and neurotransmitter synthesis.

Humans cannot synthesize folate and due to its water soluble nature, the body stores folate to a limited extent. Folate deficiency may occur when dietary intake is inadequate or when an increased need is not matched by an increased intake as:

1. conditions with a high rate of cell turnover such as rapid tissue growth (infants, kids and adolescents) pregnancy and lactation.

2. conditions such as enzyme defects, malabsorption, digestive system pathology, liver disease but also when metabolism or drug use interferes with the ability of the body to use folate.

The past decade of folate research has taught us much more about the nature of this vitamin and its critical role in supporting our health. Our goal in these next paragraphs is to provide a framework to simplify key aspects of recent research on folate and health benefits.

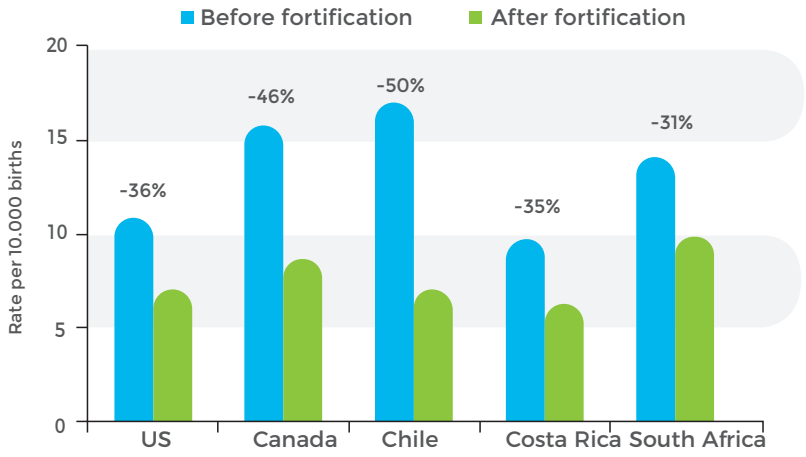
Folate and one carbon metabolism

Folate-dependent one carbon transfer is required for DNA synthesis and cell division, regulation of gene expression, amino acid metabolism and neurotransmitter synthesis.

PRECONCEPTION, PREGNANCY AND LACTATION

The demand for folate increases when human cell growth is very active, such as in pregnancy and lactation. Studies have found that low dietary intake of folate increases the risk of delivering a child with several types of birth defects, particularly neural tube defects (NTD) and possibly leading to poor growth in the fetus or placenta [29].

NTD prevalence changes before and after folic acid fortification

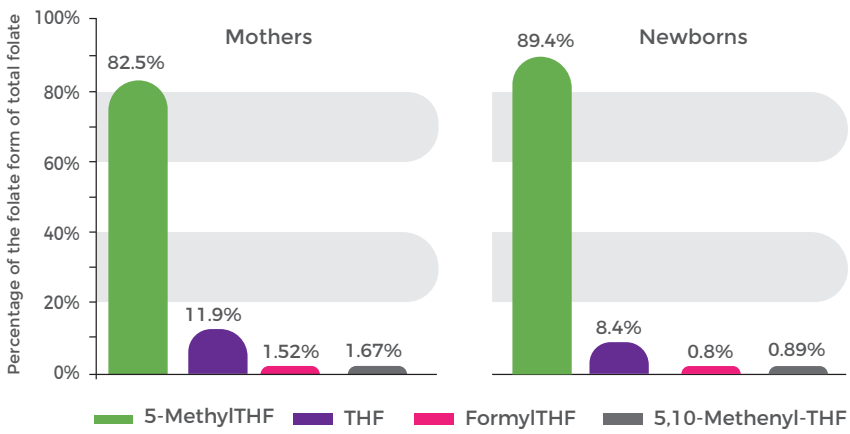


Quatrefolic® as a source of (6S)-5-methyltetrahydrofolate (5- MTHF) might be particularly useful to provide the nutritionally active form of folate during preconception, pregnancy and lactation.

The first folate choice supplementation

Quatrefolic® maximizes the benefit of folate supplementation, protecting naturally all women and babies.

Percentage of the main folate forms in maternal serum and umbilical cord serum from neonates



5-MTHF is the most available folate form in human plasma and constitutes 95–98% of folate in serum or red blood cells (RBCs). It is reversibly bound from maternal circulation by placental folate receptors (FRs) on the maternally facing chorionic surface [4,19].

Even today in Europe and United States half of pregnancies are unplanned and expose these women to a serious risk since defects of the brain and spine (Neural Tube Defects) develop in the first 28 days of pregnancy – before many women even know that they are pregnant. Clinical evidence suggests that supplementation of the natural form, 5-MTHF, is a better alternative to supplementation of folic acid, and that can effectively improve folate biomarkers in young women in early pregnancy to prevent NTDs.

Quatrefolic® may be particularly useful during preconception, pregnancy and also lactation because it provides the "natural" and "bioactive" dose of folate directly, without metabolization by MTHFR [4,19].

Spontaneous Abortion

Rapidly developing cells in the embryo may suffer by lack of adequate folate. Failure to produce sufficient DNA and to regulate DNA function could lead to spontaneous abortion [31].

Down Syndrome

Several studies have investigated maternal enzyme polymorphism in the metabolization of folate as a risk factor for Down Syndrome [32].

Lactation

Breast milk folate concentrations are maintained at the expense of maternal folate reserves. A lactating woman would require 128 µg/day of additional folate in order to restore her losses. 5-MTHF appeared to be as effective as, and perhaps more effective than, folic acid in preserving RBC folate concentrations during lactation [32,33].

WOMEN & MEN INFERTILITY

Level of folate and homocysteine status are critical factors in the early stages of human reproduction. Women and men experiencing fertility issues can present low folate availability, often linked to the presence of MTHFR polymorphism.

Methylation of DNA and fertility linked with:

- Right implantation issues
- Oocyte maturity
- Early embryo quality

Hypomethylation can cause 'Estrogen Dominance' – higher levels of the bad estrogen metabolites – can lead to disorders such as endometriosis, polycystic ovary syndrome, fibrocystic breasts, heavy bleeding/clotting, painful periods, menstrual migraines, etc.

High levels of homocysteine and low folate can make more difficult to get pregnant for women and increases the risk of early miscarriage.

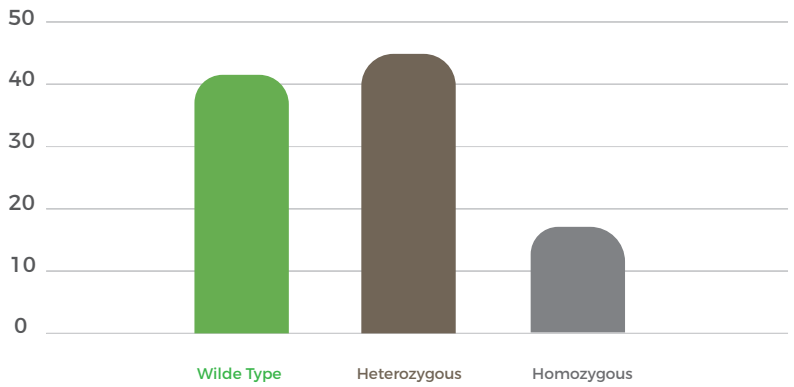
In women, folate is indispensable during the periods of rapid cell growth and proliferation, which occur during follicular and embryonic development. Insufficient folate status disrupts DNA methylation and integrity, increases blood homocysteine levels and oxidative stress one of the factors related to the pathogenesis of fertility disorders such as idiopathic infertility, polycystic ovarian syndrome and endometriosis.

Also in men, low folate levels in semen has been related to poor sperm DNA stability and damage. Folate is essential in spermatogenesis and its deficiency has been associated with low sperm count, poor sperm cell motility and morphology [34-38].

A case series study has evaluated the effect of Quatrefolic® in couples with recurrent miscarriages, lasting for at least 4 years; at least one of the partners was a carrier of one of the two main MTHFR isoforms [39].

The selected population showed a strong link between an impaired folate cycle, due to the presence of MTHFR, and consequently the capacity to achieve conception and carry a pregnancy to term. Quatrefolic® has been supplemented in men and women (with B vitamin complex and zinc) at the dosage of 800 µg/day, according to the 5-MTHF glucosamine salt requirements in healthy women. Most of the women had been previously treated unsuccessfully with high doses of folic acid (5 mg/day).

Women distribution of MTHFR polymorphism

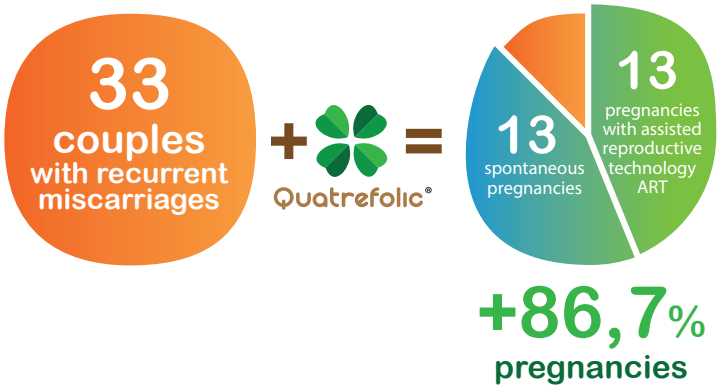


The C677T polymorphism distribution of the women population in the clinical trial is very close to what is generally observed in Europe.

5-MTHF may represent a substantial advantage in fertility issues

Quatrefolic® demonstrated to be effective in fertility both in women and men (with MTHFR polymorphism), because it is the active folate form immediately bioavailable without metabolization.

Of 33 couples, 13 spontaneous pregnancies were observed at the end of the treatment and other 13 pregnancies were obtained after assisted reproductive technology (ART), with the overall ongoing pregnancy rate of 86.7%.



The study highlights that the conventional use of large doses of folic acid (5 mg/day) has become obsolete. A physiological dose of Quatrefolic® (800 µg) bypasses the MTHFR polymorphism and is suggested to be an effective treatment for couple fertility problems [39].

WOMEN HEALTH

Contraceptive therapy

New applications and formulations suggest to combine oral contraceptives with folate because women may become pregnant during and after discontinuation of contraceptive drug treatment. Since birth control pills are the most popular method of reversible contraception in the USA, it would seem quite logical to find a way to supplement them [40].

Postpartum mood changes

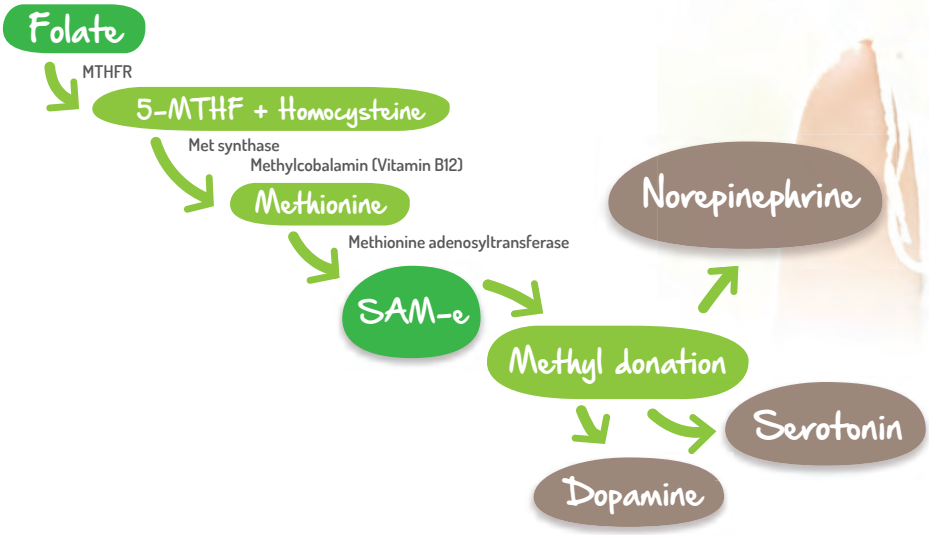
Folate deficiency can contribute to changes in mood, impairing the production on neurotransmitters through the one carbon cycle. Folate supplementation may be useful for some depressed patients [41].

Postmenopause

Whether maintained in the long term, 5-MTHF cardiovascular and metabolic effect may contribute to primary cardiovascular wellness of postmenopausal women [42].

MOOD IMPAIRMENT & DEPRESSION

Studies suggest that low levels of 5-MTHF critically contribute to reduce neurotransmitters production and increase homocysteine levels, some of the main factors that lead to onset of the mood impairment and depression. Partial- or non-responders to antidepressant drugs may be gravely folate deficient, caused by a polymorphism MTHFR, which is quite common among patients with depression. These individuals have impaired capacity to convert food folate/ folic acid into the metabolic active form, the 5-MTHF Up to 70% of patients with depression test positive for the polymorphism rendering folic acid supplements ineffective for helping in depression [43,44,45].



Supplementation of Quatrefolic® essentially bypasses the enzymatic step that may be affected, crosses the "blood-brain barrier" and enter the central nervous system, helping to restore the optimal level of brain folate.

UMFA CONCERNS: In the brain UMFA is not able to cross the Blood Brain Barrier (BBB) and may become bound to receptors (folate binding protein) on the membrane competing for cellular transport, thereby blocking the 5-MTHF bound and its absorption. Consequently, the amount of 5-MTHF crossing the BBB into the cerebral spinal fluid may be reduced, with a folate deficiency that may lead to mood dysfunction [20,21,46].

Clinical trials of folate in depression

Author	Design	Folate Supplement used	Sample characteristics	Outcome
Ginsberg et al, 2011	A retrospective analysis from patient charts 60 days	5-MTHF plus SSRI/SNRI at treatment initiation (n=95) and SSRI/SNRI monotherapy (n=147).	Adults 18 to 70 with major depressive episode (single or recurrent).	Major improvement (CGI-S reduced by ≥2 points) for 18.5 % of 5-MTHF plus SSRI/SNRI patients compared to 7.04 % (CGI-S=4-5) of SSRI/SNRI monotherapy patients.
Papakostas et al, 2012	DBC 30 days	L-MTHF (trial 1 = 7.5mg; trial 2 = 15mg) or placebo, adjunctive therapy to SSRI.	Treatment-resistant depressed patients. Trial 1, n=148 Trial 2, n=75.	7.5 mg had no significant difference. 15 mg showed significantly greater response rate and Change in HAMD score.
Reynolds et al, 2015	– 6 weeks	5-MTHF 50 mgs (25 mgs biologically active) or Amitriptyline 150 mgs.	31 patients (20 – 69 years) with a Montgomery Asberg Depression Score (MADS) of at least 14.	Of 19 patients randomised (n = 16) or crossed over (n = 3) to treatment with 5-MTHF, 8 responded (42%). Of 20 patients randomised (n = 15) or crossed over (n = 5) to Amitriptyline, 7 responded (35%) responded.

AGING, HEART & OLDER PEOPLE

Aging is associated with changes in gastrointestinal function that could possibly affect the absorption of different folate forms. This deficiency may be important with respect to blood formation, neurologic and cardiovascular function.

Epidemiological studies and case observations have suggested that low concentrations of folate in the blood can be related to poor cognitive function, dementia and Alzheimer's disease. It has been hypothesized that the relationship between folate deficiency and poor cognitive function may be due to the role of folate in reducing homocysteine blood and its effects on the vascular system. Increasingly widespread, polymorphisms of MTHFR are investigated genetic factors [47,48,49].

Cognitive Impairment

Supplementation of folate for 12 months to individuals with MCI (Mild Cognitive Impairment) was associated with significant improvements in global cognitive function compared to individuals in the conventional treatment group, particularly in memory tasks. **In a randomized, placebo-controlled trial daily folate supplementation significantly improves cognitive performance in older adults — including memory and information processing.**

The authors estimated that folate treatment gave an individual performance increase:

- **4,7 YEARS younger** — for memory
- **1,7 YEARS younger** — for sensorimotor speed
- **2,1 YEARS younger** — for information processing speed
- **1,5 YEARS younger** — for global cognitive function

Source: Durga et al. Lancet 2007

Quatrefolic®, is the only form of folate able to enter the brain without previous metabolism. Quatrefolic® passes the Brain Blood Barrier (BBB) and can support brain function also in subject with reduced metabolism of folate, due to a genetic defects of MTHFR, which impair body ability to produce 5-MTHF [50,51,52].

Cardiovascular Disease & Hyperhomocysteinemia

Homocysteinemia is widely accepted as an independent risk factor for coronary, cerebral and peripheral vascular diseases.

Molecular mechanisms of homocysteine-induced cellular dysfunction include increased inflammatory cytokine expression, altered nitric oxide bioavailability, induction of oxidative stress, activation of apoptosis and defective methylation.

Folate is an important regulator of Hcy metabolism. Clinical studies report evidence that folate supplementation can reduce cardiovascular disease risk by lowering Hcy levels.

Hcy and CVD

Elevated plasma Hcy concentration is considered a risk factor for CVD and may also be associated with hypertension.

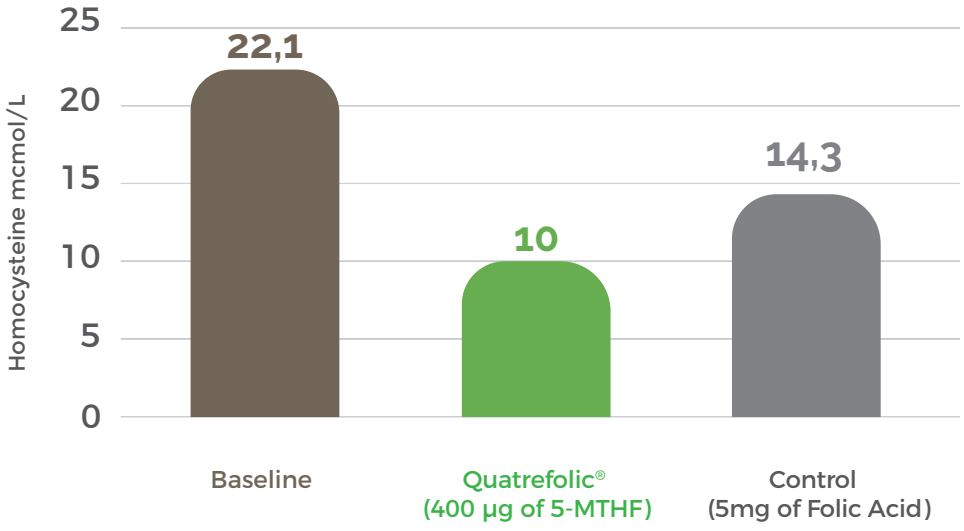
Hcy is responsible for 10% of the total risk for atherothrombotic vascular disease; a meta-analysis has highlighted that each increase of 5 µmol/L in homocysteine level raises the risk of Coronary Artery Disease (CHD) events by approximately 20%, independently of traditional CHD risk factors.

The classification of homocysteinemia

The results	Diagnosis
Normal	5 - 15 mmol/l
Mild	15 - 30 mmol/l
Moderate	30 - 100 mmol/l
Severe	> 100 mmol/l

Since the most common cause of genetic hyperhomocysteinemia (HHcy) is the 677C→T polymorphism of MTHFR, the choice of folate supplementation may differently aid to reducing Hcy levels. The effects of 5-MTHF are significantly more potent than folic acid itself as reported by Akoglu in 2008 [47,53,54].

A clinical study has demonstrated that Quatrefolic® (400 mcg plus B6 and B12) is able to lower homocysteine serum level better than conventional vitamin supplementation with highly dosed folic acid (5 mg/day).



The treatment was significantly effective and the ideal HCys level was reached in 55.8% of cases in the Quatrefolic® group, and it was significantly higher than in the control one [55].

OTHER APPLICATIONS

Anemia

Folate has a long history of use in conjunction with vitamin B12 as supplement in macrocytic anemia. Megaloblastic anemia is characterized by red blood cells that are larger than normal. The red blood cells are also deformed and both their rate of production and their lifespan are diminished.

Folate anemia occurs most often in infants, adolescents, pregnant and lactating females, alcoholics, the elderly and in those with malignant or intestinal diseases [56].

Infants & Children

Due high energy and nutrient requirements children and adolescents are vulnerable group for healthy growth and development.

Folate is a critical nutrient when human cells growth is very active and folate deficiency can slow overall growth rate. Infants, children and adolescents represent a critical phase of growth and the proper level of folate is recommended to prevent a variety of medical conditions such as anemia. Little research exists on MTHFR polymorphism and homocysteine impact on children and adolescent health and growth.

Quatrefolic® sustains healthy cell, tissue growth, digestive, and immune systems. It can improve energy production and formation of red blood cells, while promoting normal brain development and function. Moreover, the 5-MTHF can boost learning ability and memory [57].

Active lifestyle & Sport

Folate status is important both in people playing physical exercise as well as in athletes as it has a direct role in the synthesis of new cells and in the building and repairing of body tissues, including those injured due to physical activity.

Baranauskas in 2015 evaluated nutritional habits among high performance endurance athletes, finding that athletes often do not assume the Recommended Daily Allowance (RDA) of folate, with potential nutritional impairment. Since acute exercise may accelerate protein catabolism, which lead to an increase of muscular amino acid pools and homocysteine production in the methionine metabolism, active folate 5-MTHF, such as Quatrefolic®, can help to control oxidative stress and sustain cellular repair and immune system, also in people with MTHFR polymorphism [58-62].

Folate and Chronic Kidney Disease

Hyperhomocysteinemia is present in individuals with declining kidney function, so that this alteration can be considered a major factor in the progression of kidney diseases, mainly chronic kidney disease CKD. Hyperhomocysteinemia occurs in about 85% of CKD patients because of impaired renal metabolism and reduced renal excretion.

In a prospective study of 2,387 hypertensive adults, a graded association between plasma Hcy levels and an increased risk of accelerated renal function decline and incident CKD have been identified. Active folate supplementation such as Quatrefolic® may be used as an effective strategy to lower plasma Hcy levels and reduce CVD risk, limiting the deterioration of renal function, and also in curbing the cardiovascular effects of CKD [63,64].

Bone Metabolism and Health

Recent data suggest that homocysteine (Hcy), folate, vitamin B6 and vitamin B12 affect bone metabolism, bone quality and fracture risk in humans.

Different studies evaluated the effects of Hcy on bone loss from different viewpoints such as bone mineral density (BMD), fracture risk, bone markers, serum levels of vitamin B groups and the MTHFR C677T polymorphism. Recent evidence shows that Hcy directly activates osteoclast formation and activity, in vitro, via increased oxidative mechanism causing bone matrix degradation and alterations in the biomechanical properties of bone [65,66,67].

The innovACTIVE folate!

Folic acid	Quatrefolic®
Folic acid itself is not active and must be metabolized through several steps in order to enter the folate cycle.	Main folate form in blood and cord serum. It is the **biologically active form**. It can enter the folate cycle directly.
Unmetabolized folic acid is found in blood at doses >200 µg / day and may relate to potential adverse effects on human health. In the brain it can bound folate receptor blocking 5-MTHF adsorption.	**No unmetabolized** folic acid with **Quatrefolic®**, for a safe and full active folate efficacy. **Quatrefolic®** crosses Blood Brain Barrier.
Less bioavailability.	**Higher bioavailability:** Pre-clinical study in vivo with **Quatrefolic®** showed a plasmatic (6S)-5-MTHF concentration peak about **3 times higher** with **Quatrefolic®** than folic acid.
High doses of folic acid can mask vitamin B12 deficiency and delay its diagnosis by correcting hematological signs.	As **Quatrefolic®** is already the biologically active form, it doesn't mask the vitamin B12 deficiency.
Folic acid upper tolerable limit is 1mg /day.	**No upper tolerable limit of Quatrefolic®** in US dietary reference intakes. Safety of (6S)-5-MTHF has been confirmed by several studies.
5, 10-Methylenetetrahydrofolate reductase (MTHFR) enzyme polymorphism problem: In carriers of mutated homozygotes **677T->T** genotype the enzyme activity of the MTHFR is about **70% less than normal**, and heterozygotes **677C->T 30-40% less than normal**. The reduction in MTHFR activity **increases homocysteine levels and reduces the availability of the DNA methyl groups.**	**As Quatrefolic®** is already the biologically active form, **the problem of people with 677C->T or 677T->T polymorphisms in folate-related enzymes (especially MTHFR) doesn't exist anymore.**
Practically not soluble in water.	**Quatrefolic® is totally soluble in water.**
Lesser efficacy in lowering hyperhomocysteinemia.	**Quatrefolic®** it is more effective in lowering and normalizing altered homocysteine blood levels.

Quatrefolic® and 5-MTHF Calcium Salt?

(6S)-5-MTHF Ca Salt	Quatrefolic®
(6S)-5-MTHF Ca Salt is stable only at temperature between 2-8°C.	**Quatrefolic®** is lyophilized and is stable at room temperature 25°C.
(6S)-5-MTHF Ca Salt is less bioavailable.	Higher bioavailability: Pre-clinical study in vivo with **Quatrefolic®** showed a plasmatic (6S)-5-MTHF concentration peak about 20% times higher with **Quatrefolic®** than (6S)-5-MTHF calcium salt.
100 times less soluble in water than **Quatrefolic®**.	**Quatrefolic®** is totally soluble in water.
(6S)-5-MTHF Ca Salt is a crystalline salt.	**Quatrefolic®** is in **amorphous status,** offering **a higher solubility and good stability.** This guarantees an homogeneous and reproducible solubilization process compared with the crystalline alternative salt.
Solubilizing agents are often used to facilitate drying of calcium salt forms.	**No solubilizing agents** used to facilitate drying of **Quatrefolic®**.

Main health benefits of Quatrefolic®

The innovACTIVE folate!

- ✓ Women planning pregnancy
- ✓ Pregnant women
- ✓ Breastfeeding women
- ✓ Infants, children and adults with folate deficiency
- ✓ Macrocytic anemia
- ✓ Hyperhomocysteinemia
- ✓ Mood impairment & Depression
- ✓ Cognitive functions in elderly people
- ✓ Cardiovascular protection
- ✓ Sport nutrition
- ✓ Bone health

PATENTS:

"Folates, compositions and uses thereof." (U.S. Patent No. 7,947,662 – European Patent No. EP 2245032) "Process for the diastereoisomeric resolution of 5-methyltetrahydrofolic acid." (EP 2254890 - PCT/EP2008/52034)

TRADEMARK:

Quatrefolic® trademark and four-leaf clover logo is a proprietary trademark of Gnosis by Lesaffre

LEGISLATION AND COMPLIANCE:

- Manufacturing Operations FDA Inspected
- HACCP
- 21CFR Part 111

CERTIFICATIONS:

- UNI EN ISO 22000:2500
- KOF-K Certificate
- Halal Certificate

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