



# Why the active form of folate is preferred

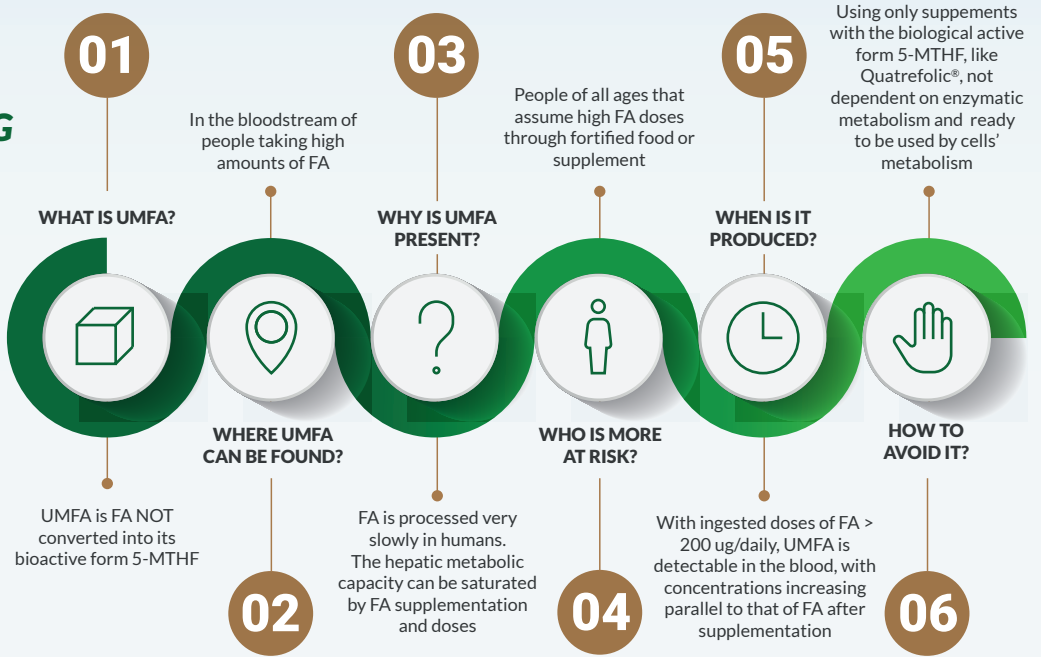


## Active Folate and UMFA (UnMetabolized Folic Acid)

### 5-MTHF and FOLIC ACID ARE NOT THE SAME THING

**Folic acid (FA)** is a synthetic form of vitamin B9, and it is not biologically active.

**Quatrefolic®** is the active form of folate readily available for transport and use in the human body and tissues.

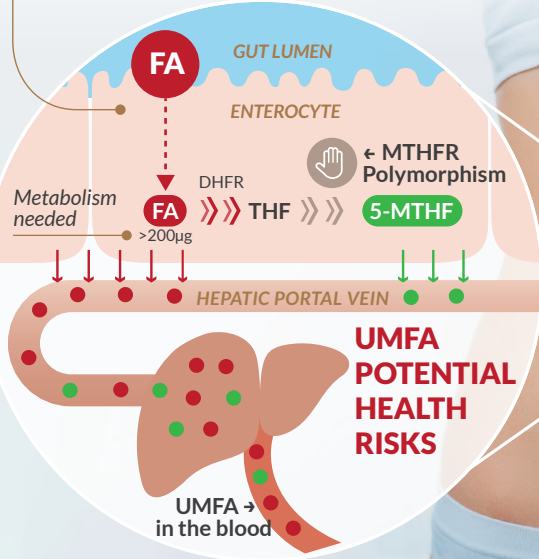


## How does Folic Acid generate UMFA in the bloodstream?

The human gut appears to have a limited ability to reduce FA, and the largest physiologic oral dose of FA passes into the portal venous circulation in an unmodified form. Biotransformation of FA to 5-MTHF is critically regulated by Methylene tetrahydrofolate reductase (MTHFR) enzyme of which the incidence of MTHFR is around 40% in the global population.

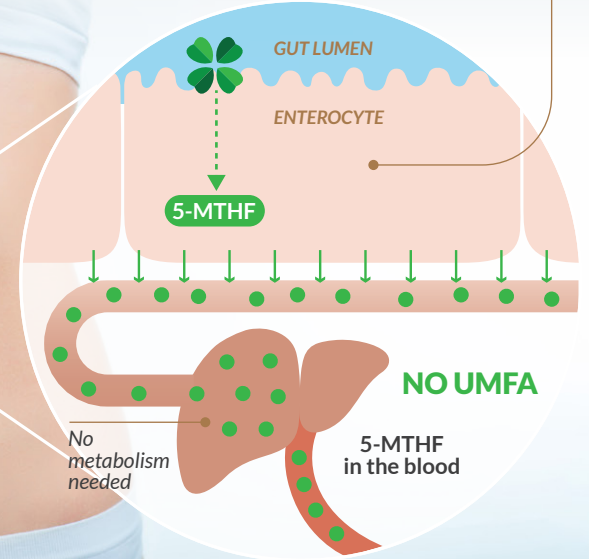
### FOLIC ACID SUPPLEMENTATION

Enterocytes show inadequate activity to convert FA into active folate (5-MTHF)



### QUATREFOLIC® SUPPLEMENTATION

5-MTHF is absorbed by enterocytes, later enters the liver, and finally the systemic circulation to exert the biological effect



## How Prevalent is UMFA?

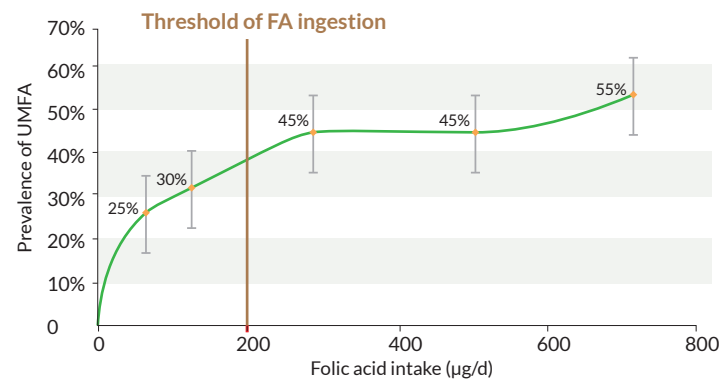
Even in countries without mandatory fortification, UMFA is detectable in blood, be it from fortified foods or use of folic acid supplements.

**23%** of general population  
**78%** of fasting postmenopausal women  
**43%** of children aged 5y  
**38%** of the elderly

## Does UMFA Warrant our Attention?

UMFA presence in systemic circulation and its build-up due to FA supplementation may be correlated with potentially harmful effects

UMFA percentage in the blood increasing FA ingestion



### UMFA RISKS

- UMFA could reduce the immune system efficacy
- Increased food allergy among children with higher concentrations of UMFA at birth
- UMFA does not cross Blood-Brain Barrier and competes with the cellular transport of 5-MTHF in the brain
- UMFA can contribute to cognitive- and immune-related problems

## Folic Acid

<b>Form</b>	Oxidized synthetic compound	Glucosamine salt of the reduced 5-MTHF active form
<b>Biological Activity</b>	Biologically inactive in the human body	Biologically active and predominant folate form in human plasma
<b>Metabolization</b>	Requires multi-step enzymatic conversion to become active and be used by the body	Does not require metabolization as it is ready to perform its biological role
<b>UMFA risk</b>	Doses of >200ug/day can present UMFA in systemic circulation	No accumulation of UMFA in the blood
<b>Health risk</b>	UMFA is known for potential toxic effects on human health	No health risk
<b>Dosage limit</b>	Upper tolerable limit of folic acid is 1000 µg/day	No upper tolerable limit for 5-MTHF

Obeid R, Herrmann W. *Curr Drug Metab.* 2012;13(8):1184-1195.  
Bailey SW, Ayling JE. *Proc Natl Acad Sci U S A.* 2009;106(36):15424-15429.  
Smith AD et al. *Am J Clin Nutr.* 2008;87(3):517-533.  
Ulrich CM et al. *Cancer Epidemiol Biomarkers Prev.* 2006;15(2):189-193.  
Ulrich et al. *Cancer Epidemiol Biomarkers Prev* 2006;15:189-193

Kelly et al. *Am J Clin Nutr.* 1997;65:1790-5  
Vincickier, AK et al. *Nutrients.* 2021;13(5):1557.  
Patanwala I et al. *Am J Clin Nutr.* 2014;100(2):593-599.  
Pietrzik K et al. *Clin Pharmacokinet.* 2010;49(8):535-548.  
Paniz C et al. *J Nutr.* 2017;147(9):1677-1685.

McGowan et al. *J Allergy Clin Immunol Pract.* 2020;8(1):132-140.e5.  
Han YY et al. *J Allergy Clin Immunol.* 2020;146(1):220-222.e8.  
Sweeney MR et al. 2007;7:41.  
Sweeney MR et al. *Br J Nutr.* 2006;95(1):145-151.

Obeid R. *J Nutr.* 2015;145(3):387-390.  
Bailey RL et al. *Food Nutr Res.* 2012;56  
Serum folate metabolites, asthma, and lung function in a nationwide US study - *Journal of Allergy and Clinical Immunology (facionline.org)*