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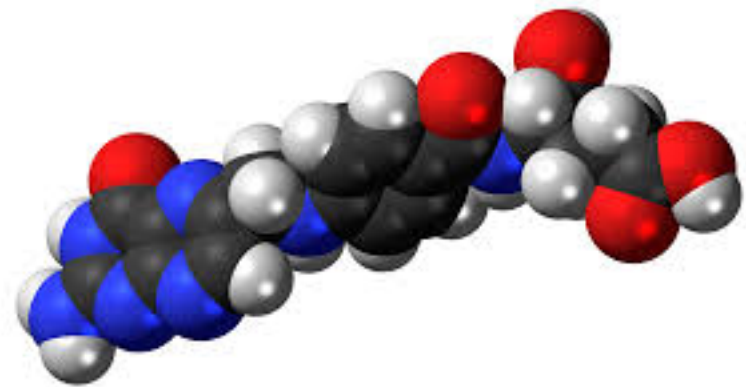
[people.csail.mit.edu/seneff/2015/  
WAPF\\_folate.pptx](http://people.csail.mit.edu/seneff/2015/WAPF_folate.pptx)

# Folic Acid Supplementation: Why This is Not a Good Idea

Stephanie Seneff

WAPF

Sunday, Nov. 15, 2015



"I think we risk becoming the best-informed society that has ever died of ignorance."

Rubén Blades

*“It is simply no longer possible to believe much of the clinical research that is published, or to rely on the judgment of trusted physicians or authoritative medical guidelines. I take no pleasure in this conclusion, which I reached slowly and reluctantly over my two decades as editor of the New England Journal of Medicine.”*

Marcia Agnell.

# THIS IS THE NEW CHILDHOOD IN AMERICA:

- 1 in 3 is overweight
- 1 in 6 has learning disabilities
- 1 in 9 has asthma
- 1 in 10 has ADHD
- 1 in 12 has food allergies
- 1 in 20 has seizures
- 1 in 54 males has autism

1 in 45!

tism

50% (half) of all children have chronic illness or are overweight.

This is the NEW NORMAL in our country.

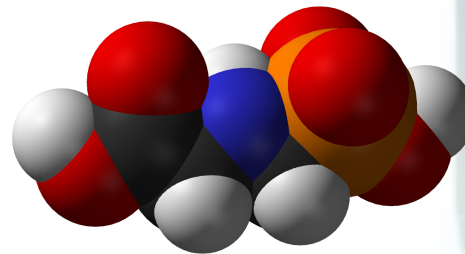
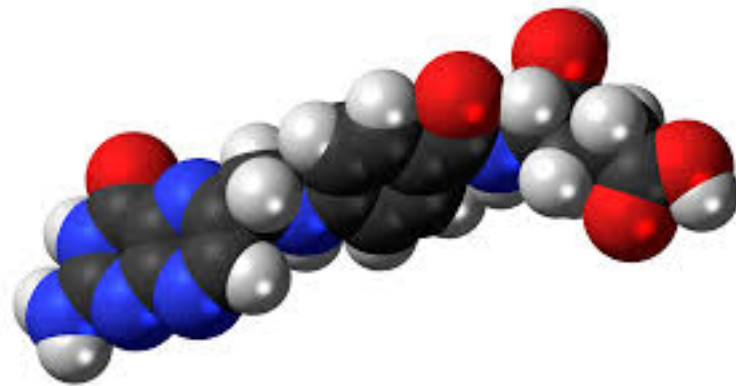
Are you concerned yet?!  
Because if you're not,  
then you are not paying attention!



# Outline

- Glyphosate and Folic Acid
- Folic Acid Biology
- Evidence of Harm
- Interaction with Minerals
- What you can do!
- Summary

# Glyphosate and Folic Acid



# The Big Picture\*

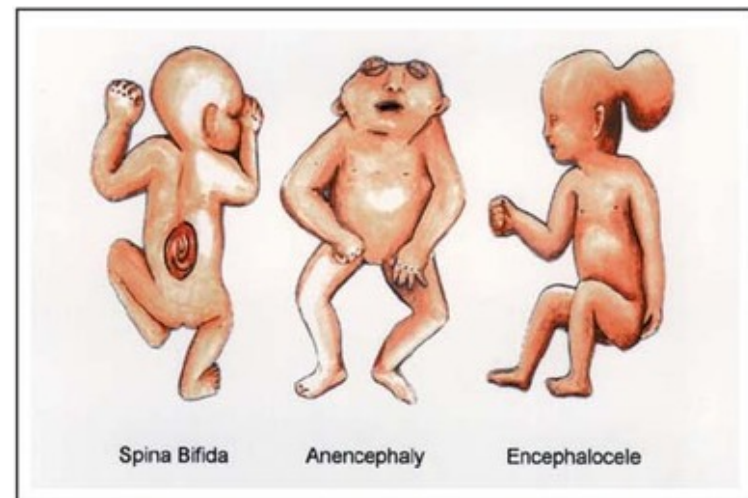
- Synthetic folic acid is different from natural folate in important ways
  - Excess supplementation leads to high circulating doses in the blood
  - Alters the functions of hundreds of genes
  - One obvious effect is low birth weight → autism
- Children with autism were more likely to have mothers taking folic acid supplements during pregnancy
- Folic acid supplementation alone can lead to the dysregulation of over 1000 genes

\*MC DeSoto and RT Hitlan, Journal of Pediatric Biochemistry 2 (2012) 251–261



# A Bit of History

- Neural tube developmental defects like spina bifida and anencephaly (no brain) are due to a very rare but catastrophic developmental disorder linked to low folate during the first trimester of pregnancy
- Excess retinoic acid expression during development causes neural tube developmental defects
- The US first considered adding folic acid supplements to grains in 1996, and introduced the mandate in 1998
- GMO “Roundup Ready” crops were just beginning to be introduced in 1996 and had obtained widespread adoption by 1998



# Adoption of “Roundup Ready” Crops\*

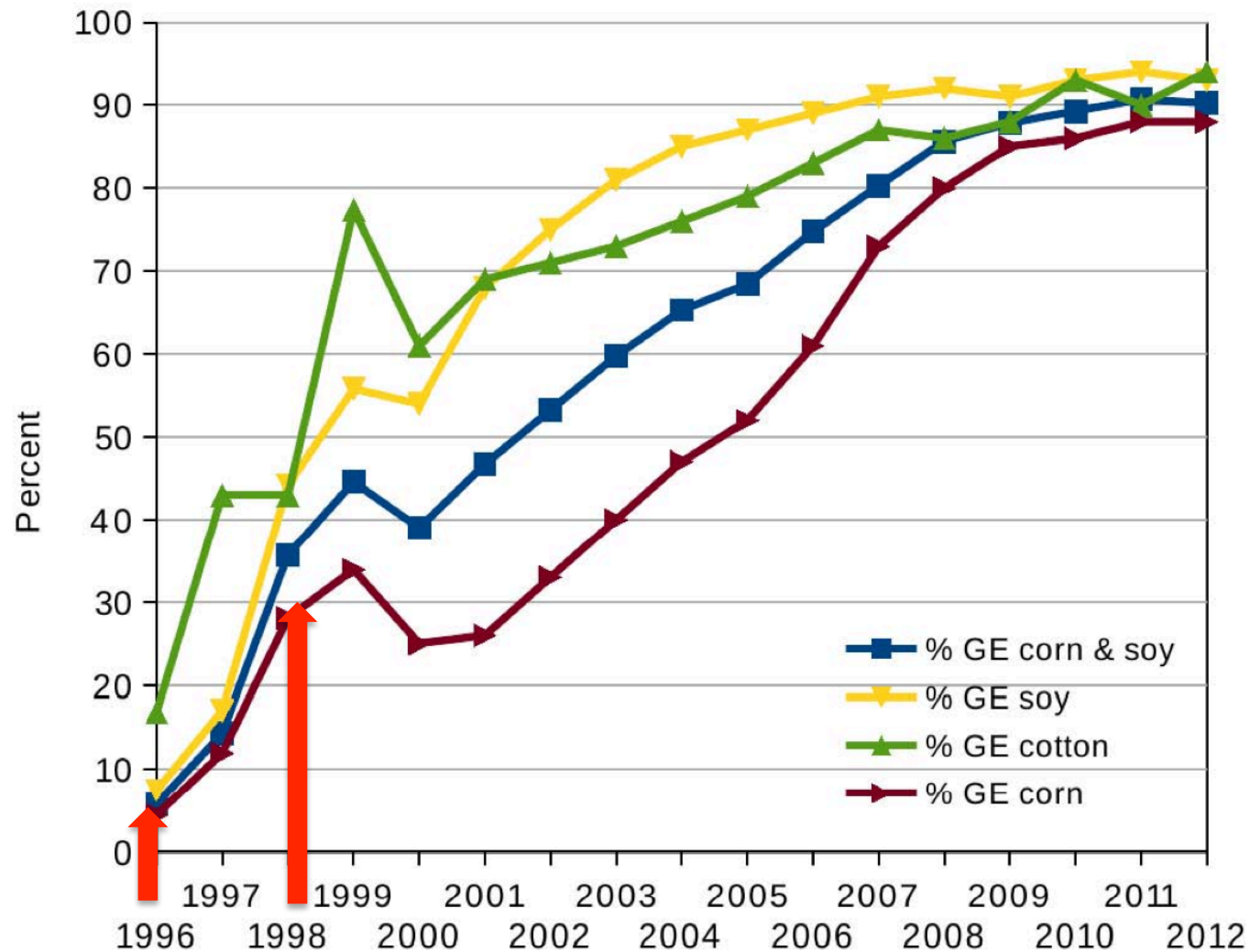
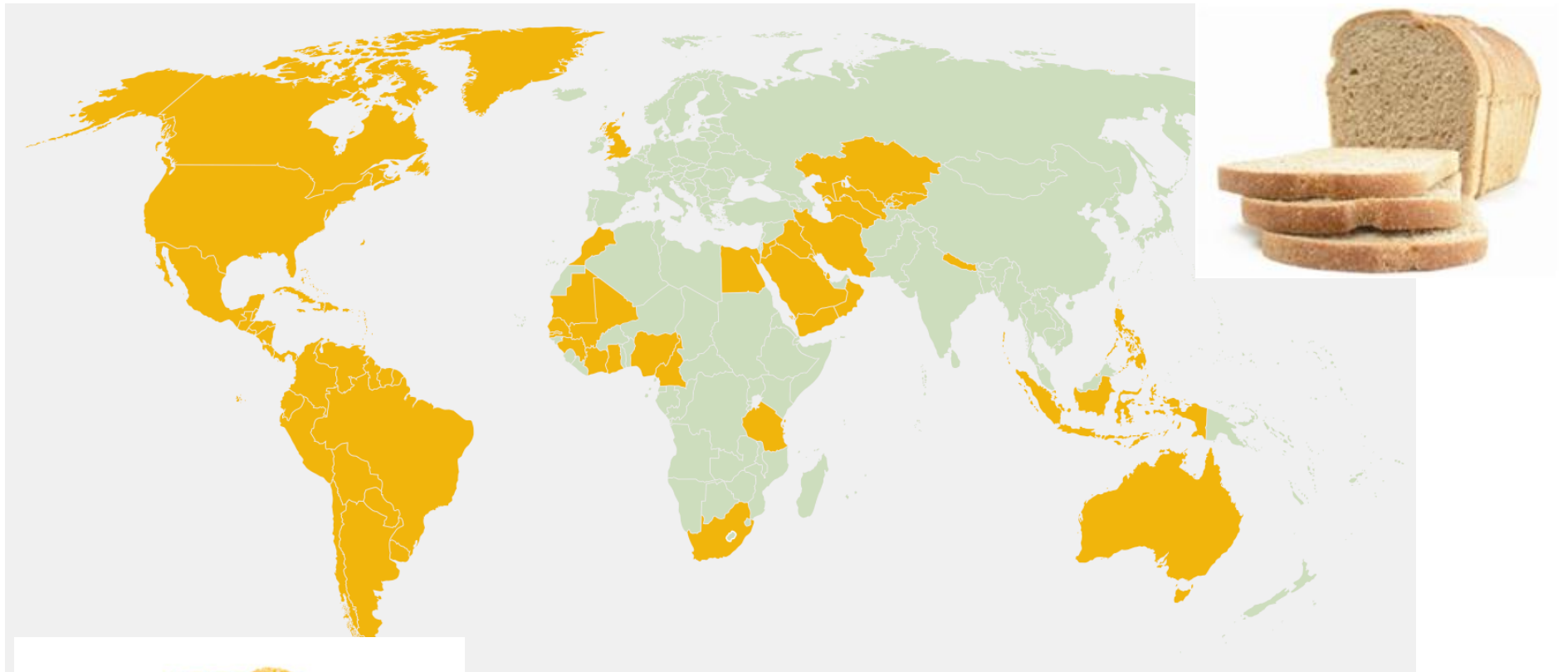


Figure 1. Adoption of GE crops in US.

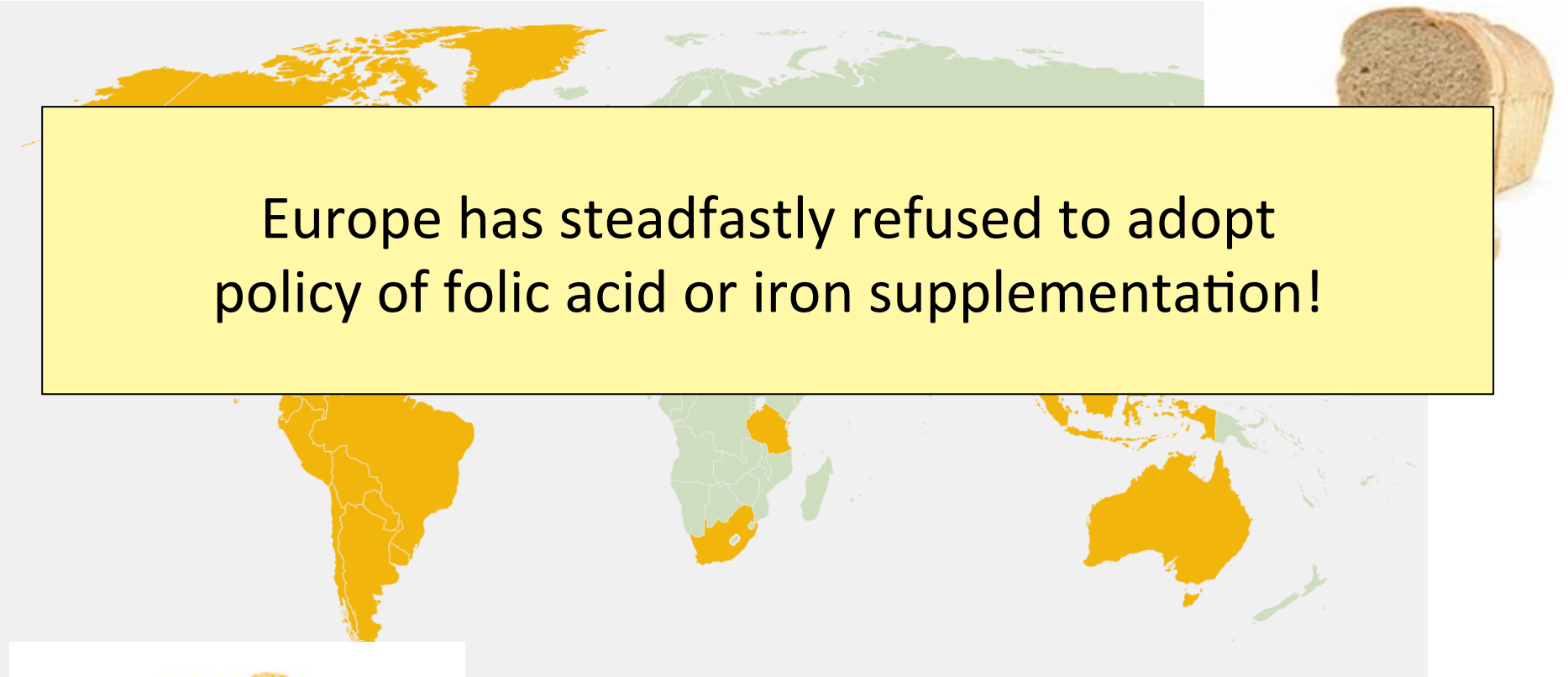
\* N. Swanson et al., Journal of Organic Systems 20145;9(2): 6-37.

# Folic Acid and/or Iron Fortification\*



\*B Handforth and S. Zimmerman,  
Sight and Life 27 (1); 70-75, 2013

# Folic Acid and/or Iron Fortification\*



Europe has steadfastly refused to adopt policy of folic acid or iron supplementation!



\*B Handforth and S. Zimmerman,  
Sight and Life 27 (1); 70-75, 2013

# U.S. Regulation on Wheat\*

**TITLE 21--FOOD AND DRUGS; Subpart B:**  
Requirements for Specific Standardized Cereal  
Flours and Related Products

## **Sec. 137.165 Enriched flour.**

a) It contains in each pound 2.9 milligrams of thiamin, 1.8 milligrams of riboflavin, 24 milligrams of niacin, *0.7 milligrams of folic acid, and 20 milligrams of iron.*

\*<http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=137.165>

# Factors in Celiac Disease?

- We have an epidemic in gluten intolerance and celiac disease today in the U.S.
- Wheat products contain added folic acid and added iron
- Wheat is often sprayed with glyphosate right before the harvest
- Do these three factors work synergistically to contribute to celiac disease?

# Glyphosate and Anencephaly\*

- Yakima, Benton and Franklin counties in Washington State have an unusually high number of pregnancies affected by anencephaly
- 75 pesticides were analyzed in studying contamination due to surrounding agriculture
  - 47 (63%) of these were detected
  - Glyphosate was applied in large amounts, *but was not studied*
- 5% solution of glyphosate was also used heavily around irrigation ditches to control weeds
  - Main herbicide recommended due to its “low toxicity”



\*Barbara H. Peterson. *Farm Wars*, <http://farmwars.info/?p=11137>

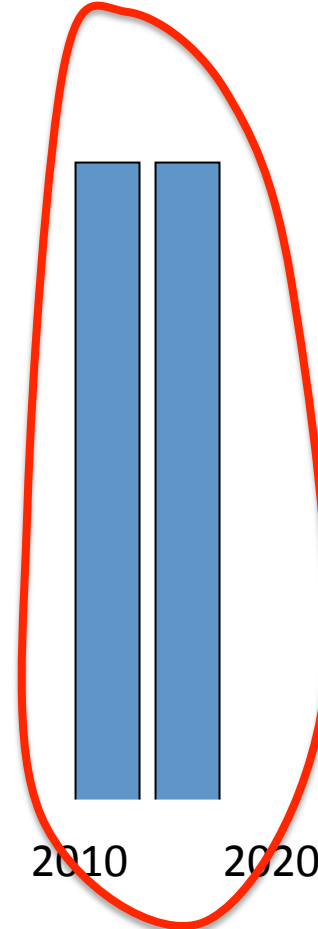
# “Glyphosate, Brain Damaged Babies, and Yakima Valley - A River Runs Through It”\*



Noxious aquatic weed control program with Glyphosate ‘Rodeo’



1980 1990 2000 2010 2020



## “Glyphosate, Three Rivers, and Anencephaly”

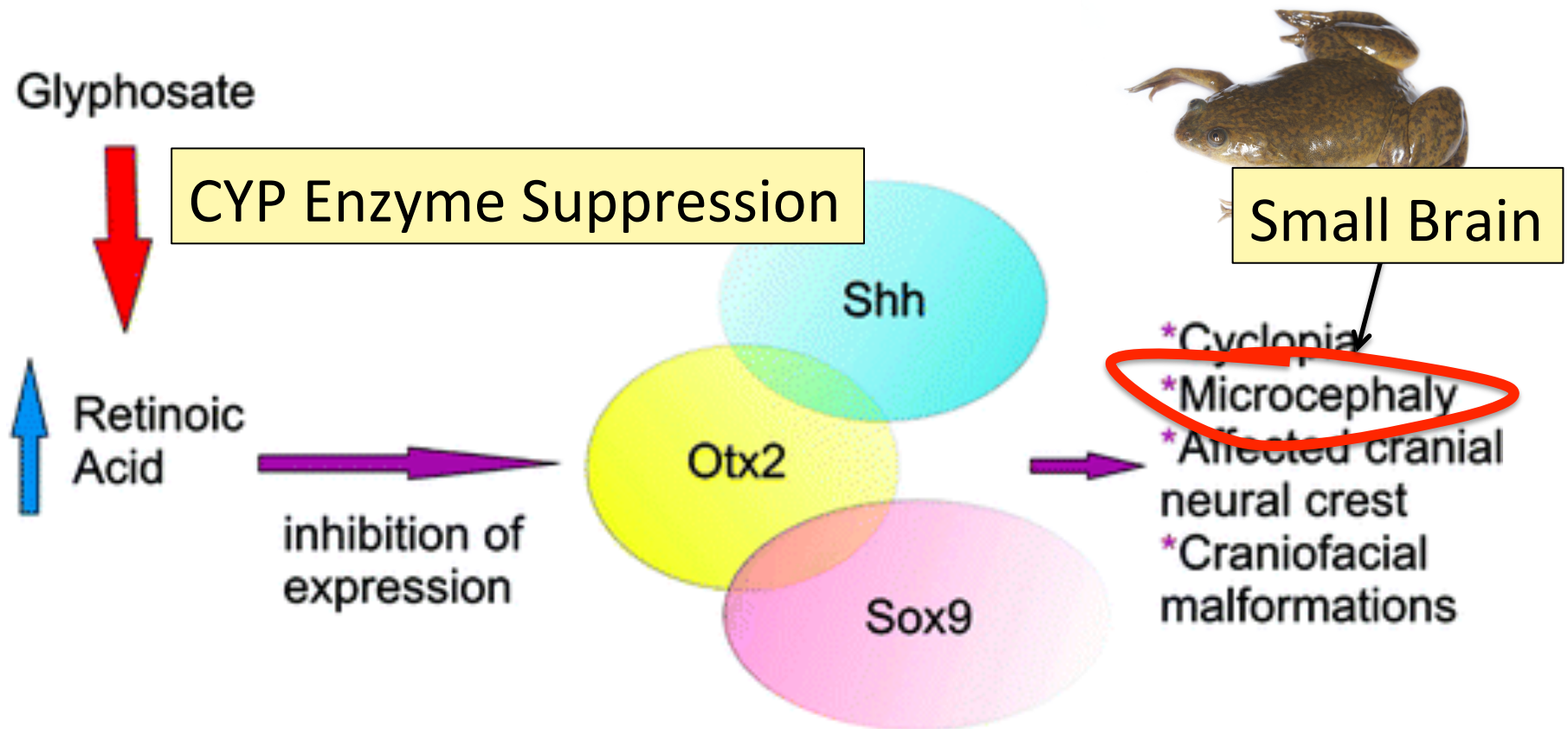
Yakima Harold Republic

Slide thanks to Prof. Don Huber, with permission

\*Farm Wars 3/6/14



# Glyphosate Upregulates Retinoic Acid\*



\*A. Carrasco, Teratogenesis by glyphosate based herbicides and other pesticides. Relationship with the retinoic acid pathway. In Breckling, B. & Verhoeven, R. (2013) GM-Crop Cultivation – Ecological Effects on a Landscape Scale. Theorie in der Ökologie 17. Frankfurt, Peter Lang.

# Gut Microbes Provide Folate to Host!\*

“In conclusion, the findings from this study suggest that the quantity of *microbially synthesized folate* in the large intestine of human infants is sufficiently large to potentially affect the folate status of the host. The results of the analysis ... suggest that a significant fraction of folate is in a form (monoglutamylated) that can be readily absorbed. “

\*TH Kim et al., J Nutr. 2004 Jun;134(6):1389-94.

# Gut Microbes Produce Bioavailable Folate\*

- Strains of lactobacillus and bifidobacteria were shown to synthesize folate
  - Both of these are especially susceptible to glyphosate toxicity
- "Rats fed a probiotic formulation of folate-producing bifidobacteria exhibited increased plasma folate level, confirming that the vitamin is produced in vivo and absorbed"

\*M Rossi et al., Nutrients 2011, 3, 118-134

# Gut Microbes Produce Bioavailable Folate\*

- Strains of lactobacillus and bifidobacteria

Glyphosate disrupts the shikimate pathway in gut microbes.

- Folate, produced by gut microbes, depends on the shikimate pathway

vitamin is produced in vivo and absorbed"

\*M Rossi et al., Nutrients 2011, 3, 118-134

# US Aggressive Campaign: A Down Side to Folic Acid?

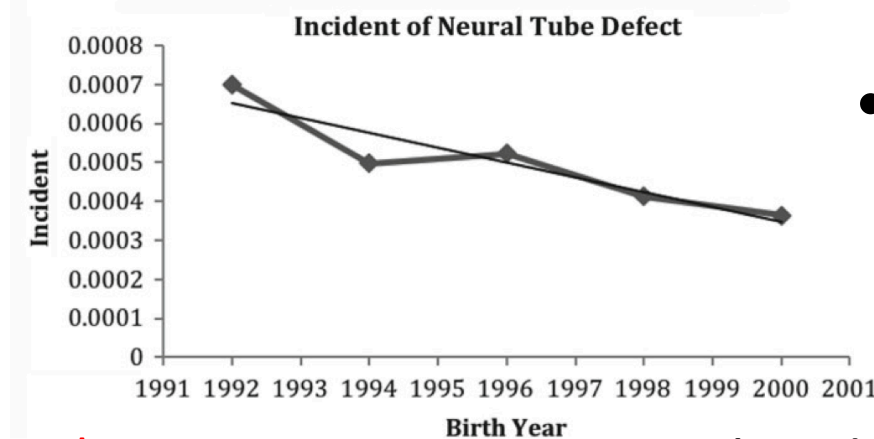
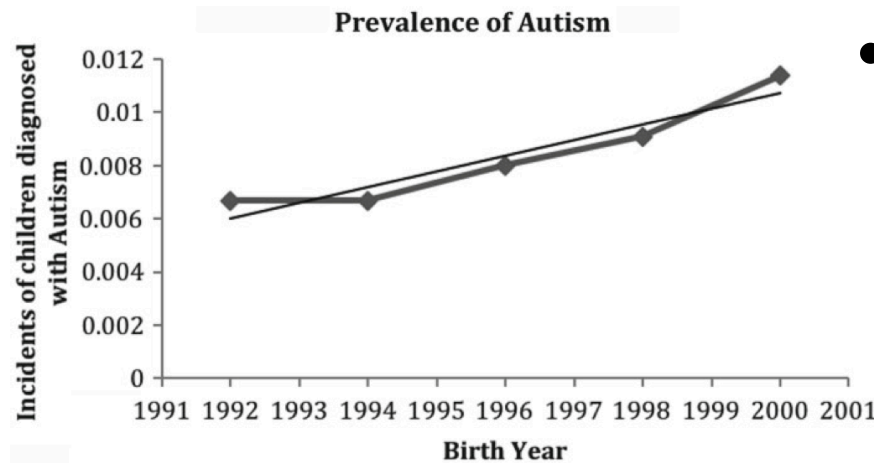
- In addition to fortification, US FDA recommends folic acid (FA) supplements for women of childbearing age
- However, excessive FA supplementation has been linked with increased incidences of asthma\* and autism\*\* among children.



\*MB Bekkers et al. Eur Respir J 2012;39(6):1468–1474.

\*\*CM Beard et al, Med Hypotheses 2011;77(1):15–17.

# Inverse Correlation Between Neural Tube Defects and Autism Trends\*



- Proposed mechanism involves increased GABA receptor activity (neuronal inhibition)
- GABA increase has been linked to autism\*\*

\* Figure 4, K. Vasquez et al., Adv Exp Med Biol. 2013;775:101-9.

\*\* SH Fatemi et al., J Autism Dev Disord 2010;40(6):743–750.

# How much folic acid is too much?\*

- For children < 8 years old -- tolerable upper limit set at 300-400 mcg.
- One cup of breakfast cereal has 400 mcg
- > 10% of pregnant women are taking > 1000 mcg/day folic acid supplements on top of dietary folic acid fortification
- Natural folate found in food sources has never been a problem

\*NIH Dietary Supplement Fact Sheet: Folate  
<http://ods.od.nih.gov/factsheets/folate>

# **“Folate, vitamin B12 and homocysteine in relation to birth defects and pregnancy outcome”\***

"However, intervention with folic acid alone may not only be inefficient, but may even cause harm to women living in regions where vitamin B12 deficiency is endemic. The scientists, clinicians and policy-makers in different countries should carefully investigate and evaluate the relevance of the present guidelines in their own populations."

\* H Refsum, British Journal of Nutrition (2001), 85, Suppl. 2, S109±S113.



# Folic Acid Biology

# “Folic acid fortification: the good, the bad, and the puzzle of vitamin B-12”\*

- Low B-12 (cobalamin) / High folic acid →
  - 5-fold increased risk to anemia
  - 5-fold increased risk to cognitive impairment
  - 4% of elderly tested met this criterion
- ~1.8 million elderly might be at increased risk of cognitive impairment and anemia because of an imbalance between folate and vitamin B-12.

\* A David Smith, Am J Clin Nutr 2007;85:3-5.

# “Folic acid fortification: the good, the bad, and the puzzle of vitamin B-12”\*

- Low B-12 (cobalamin) / High folic acid →

"Is it ethical to save one infant from developing a neural tube defect but increase the risk of poorer health in ~1000 elderly persons?"

cognitive impairment and anemia because of an imbalance between folate and vitamin B-12.

\* A David Smith, Am J Clin Nutr 2007;85:3-5.

# What's the difference between folic acid and folate???

- Folate is the form of the B vitamin that is found in nature: you can never overdose on it
  - Folate is typically methylated
- Folic acid is a *synthetic* molecule, and it's stable
- Folic acid is missing four hydrogen ions –  
*THIS IS VERY IMPORTANT!!!*

Folic acid is *oxidized*, and to convert it to folate is costly for the body

# Folic Acid is Complex

- Folic acid is a synthetic, oxidized form of folate
- It induces oxidative stress in the liver
- This can lead to folic acid build-up (unnatural) in the blood
- This interferes with nitric oxide release which is important for promoting blood flow
- Folic acid in the blood may also cause the antibodies to folate receptors in the brain associated with cerebral folate deficiency

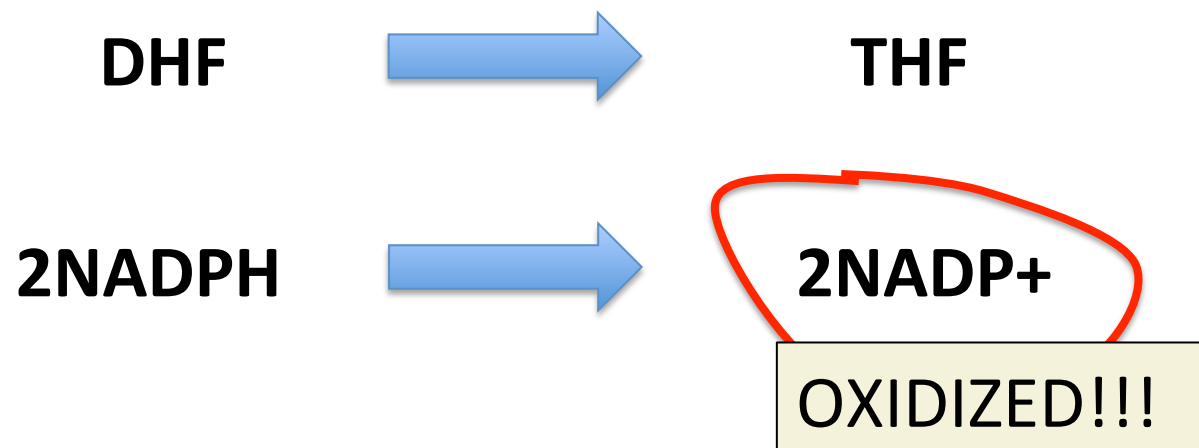
# Crucial Difference between Folic Acid and Folate\*

“Unlike natural folates, which are metabolized to THF in the mucosa of the small intestine, folic acid undergoes initial reduction and methylation in the liver, where conversion to the THF form requires dihydrofolate reductase. The low activity of this enzyme in the human liver, combined with a high intake of folic acid, may result in unnatural levels of unmetabolized folic acid entering the systemic circulation.”

\*<http://chriskresser.com/folate-vs-folic-acid>

# In the Liver...\*

**Dihydrofolate reductase** reduces dihydrofolic acid (**DHF**) to tetrahydrofolic acid (**THF**) using NADPH as electron donor



\*[http://en.wikipedia.org/wiki/Dihydrofolate\\_reductase](http://en.wikipedia.org/wiki/Dihydrofolate_reductase)

# eNOS needs NADPH, NOT NADP+!!

L-arginine + H<sup>+</sup> + 2 O<sub>2</sub> + 3/2 NADPH



citrulline + nitric oxide + 3/2 NADP<sup>+</sup>



Relaxes blood vessels; promotes flow

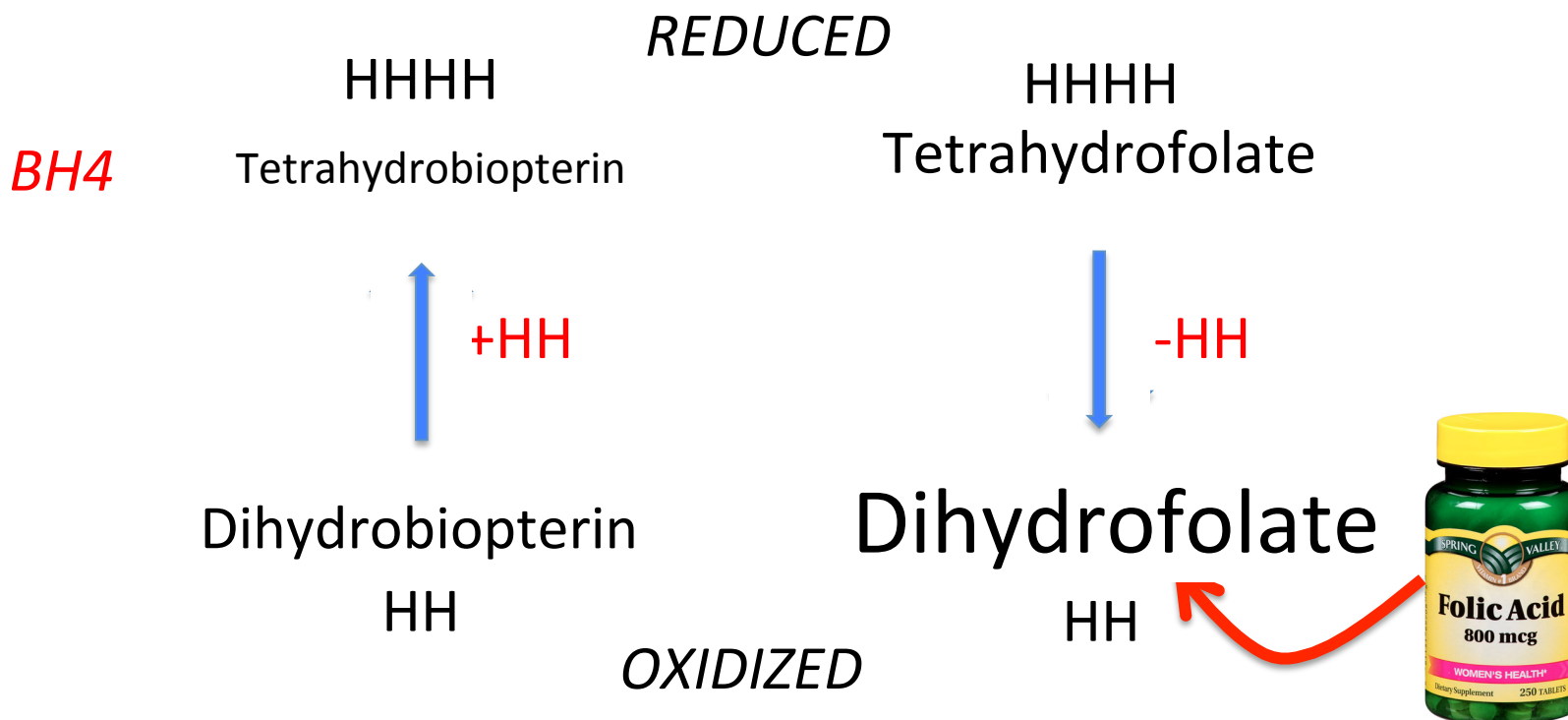


# Consequences

- Liver ends up with NADP<sup>+</sup> rather than NADPH
- Methyl groups get depleted in the liver
- eNOS is unable to synthesize adequate nitric oxide → constricted blood vessels; poor oxygen supply
- Unmetabolized folic acid ends up in the blood and can bind to receptors in the brain, messing up brain folate homeostasis (more later)

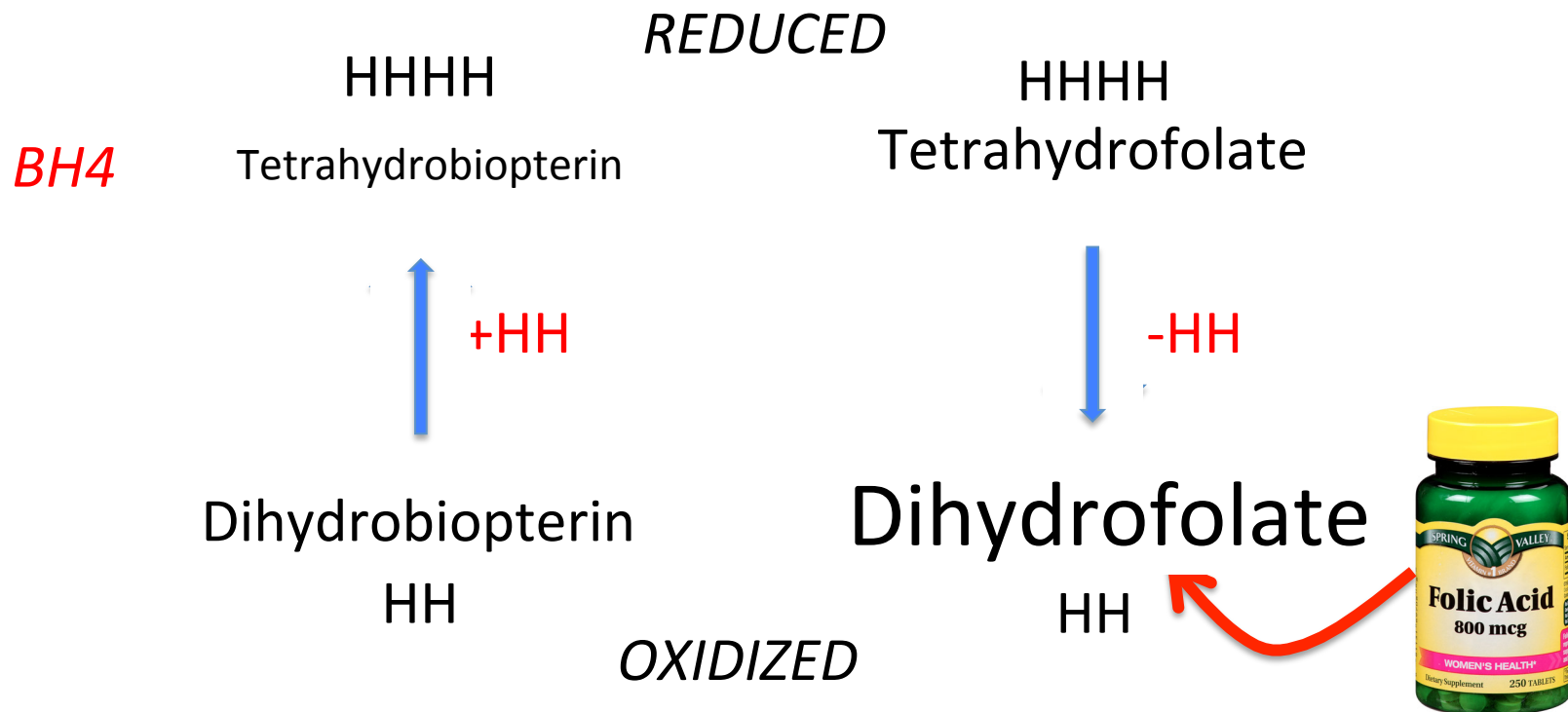
# A Problem with Folic Acid

Excess folic acid drives biopterin towards the oxidized form, which is not good!



# A Problem with Folic Acid

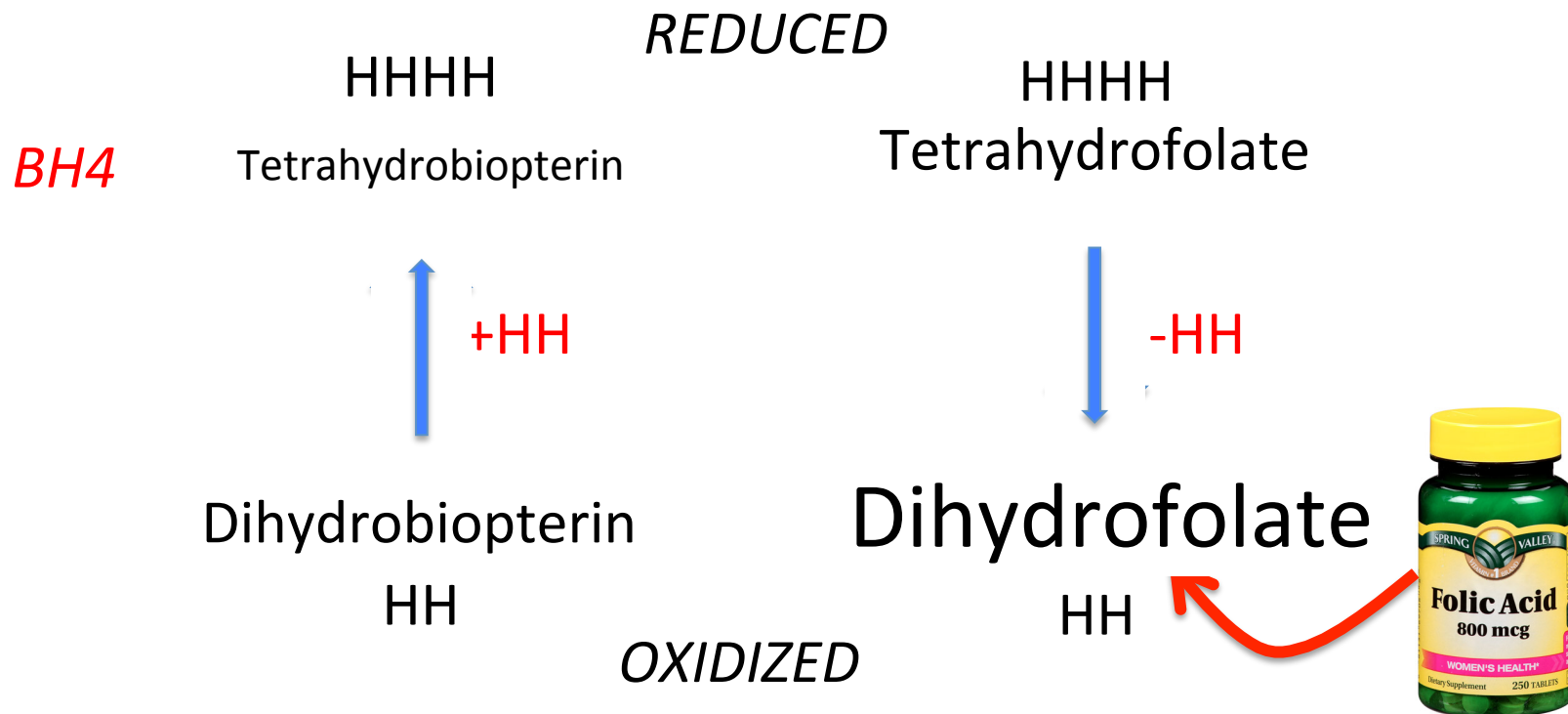
Low BH4 in the cerebrospinal fluid is linked to autism\*



\*RE Frye et al., Neurotherapeutics. 2010 July ; 7(3): 241–249.

# A Problem with Folic Acid

BH4 is essential for nitric oxide release, which promotes blood flow



\*RE Frye et al., Neurotherapeutics. 2010 July ; 7(3): 241–249.

# eNOS Requires BH4 to Synthesize Nitric Oxide\*

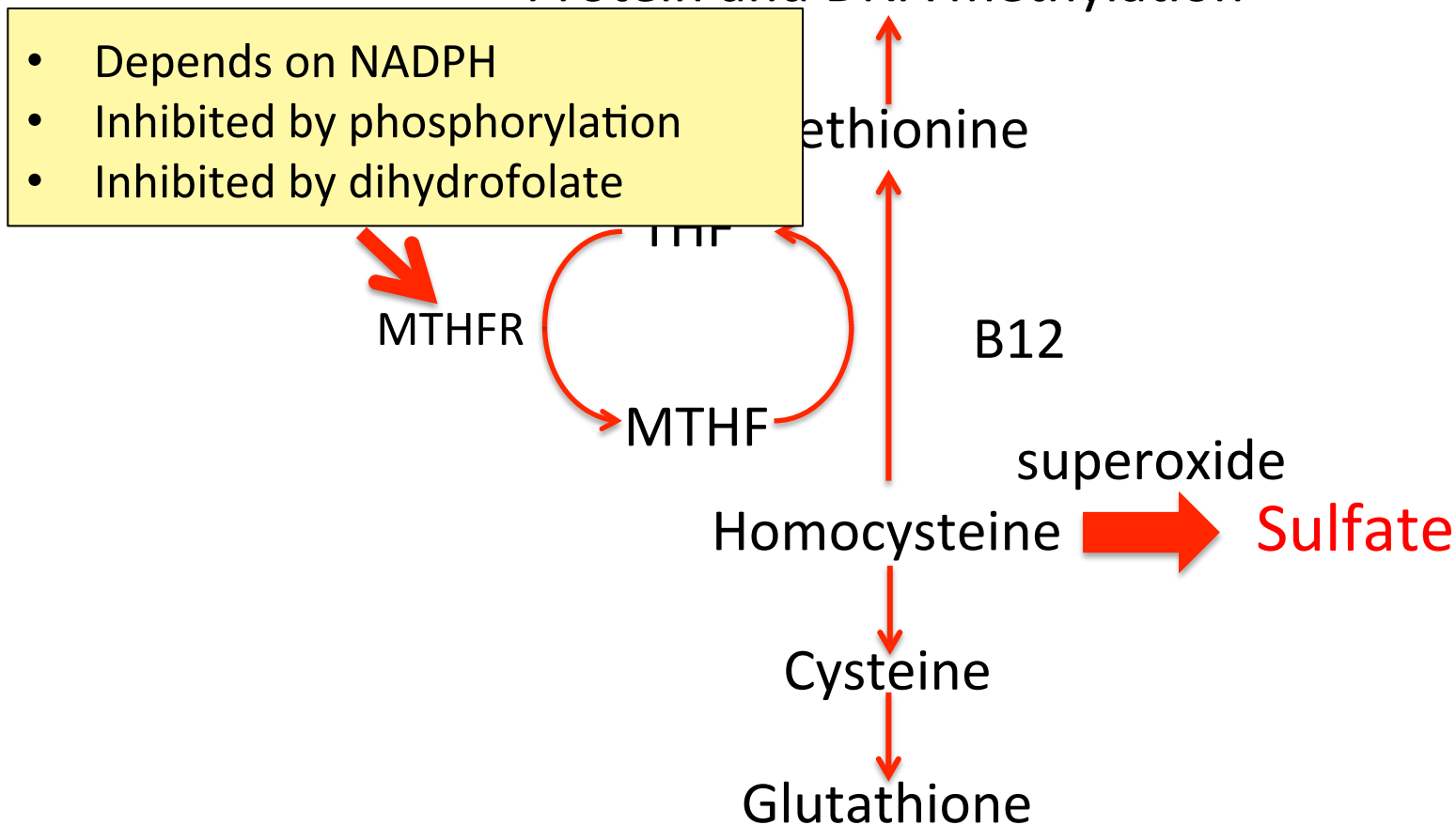
- BH4 catalyzes the reaction that produces nitric oxide by breaking down L-arginine
- When BH4 is depleted, eNOS produces superoxide ( $O_2^-$ ) instead
- Superoxide causes oxidative damage and is a major source of reactive oxygen
  - BUT: it is needed to synthesize sulfate!!!

\*T Scott-Burden, Circulation 1995; 91: 248-250.

# Simplified Methyl Cycle

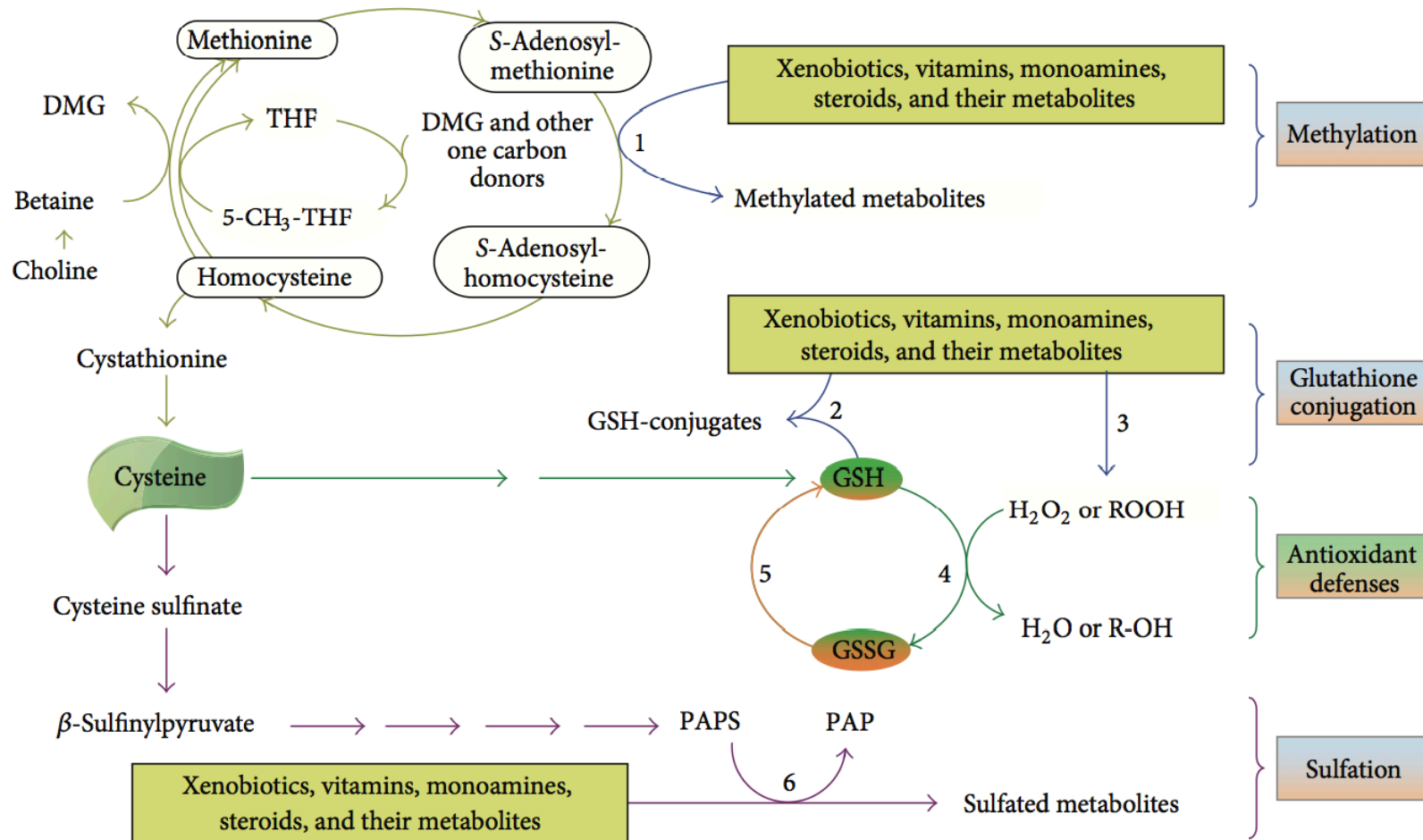
MTHFR gene variants linked to autism\*

Protein and DNA methylation



\*M Boris et al., Journal of American Physicians and Surgeons 2004;9(4): 106-108.

# Too Many Vitamins!



\*Figure 2, S-S Zhou et al., Autism Research and Treatment 2013, Article ID 963697

# Generating Methionine from Homocysteine

Folate trap: One or more of these requirements are missing; Methyl group stays stuck on folate (inactive)

There is a belief that elevated serum homocysteine is bad, but the homocysteine is desperately needed to produce sulfate

Methionine

*Methionine synthase*



Homocysteine

**Requirements:**

Working MTHFR enzyme

Cobalamin (vitamin B12)

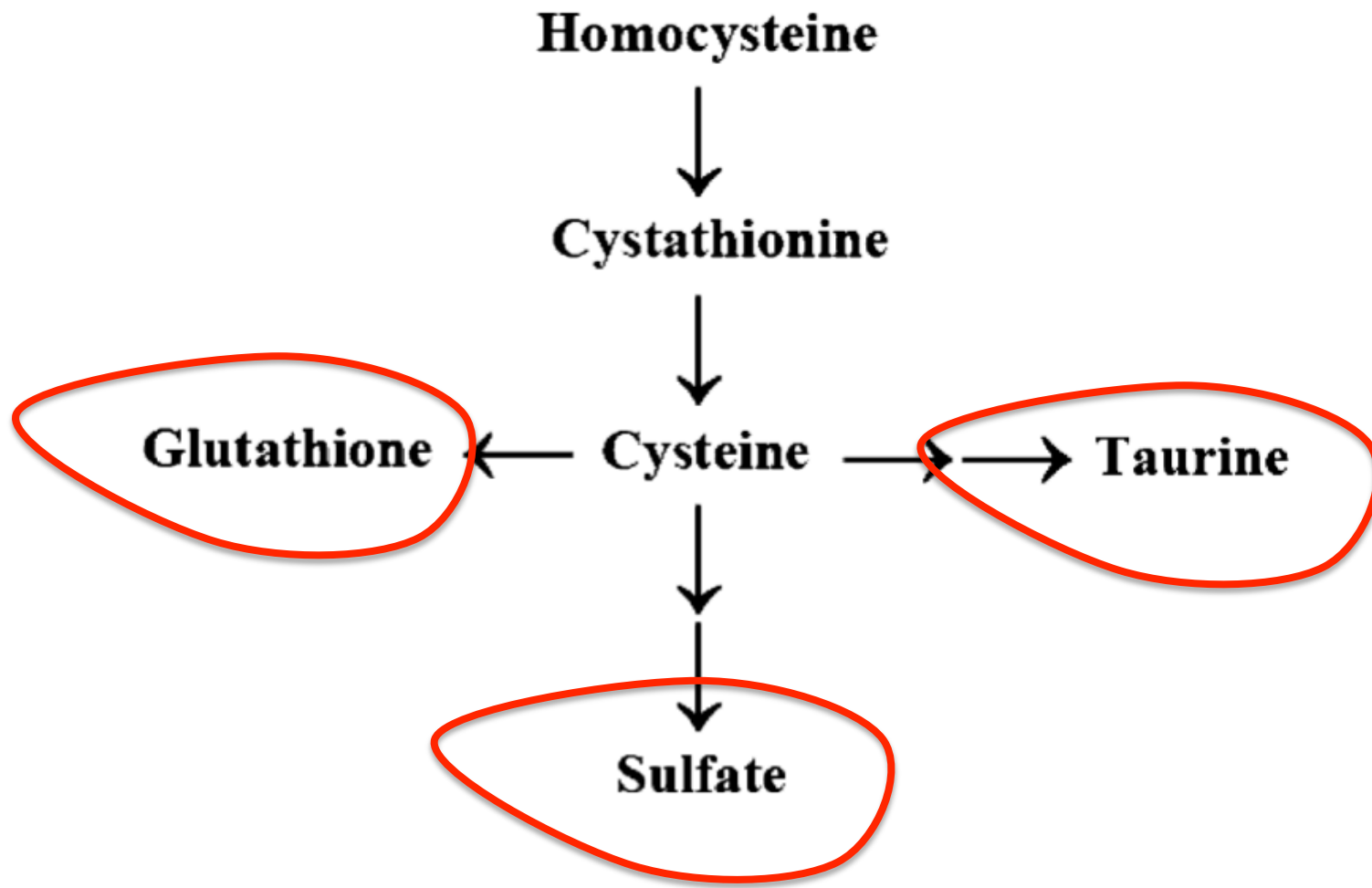
Zinc

Vitamin B6

**Methyl tetrahydrofolate**



# Transsulfuration Pathway\*

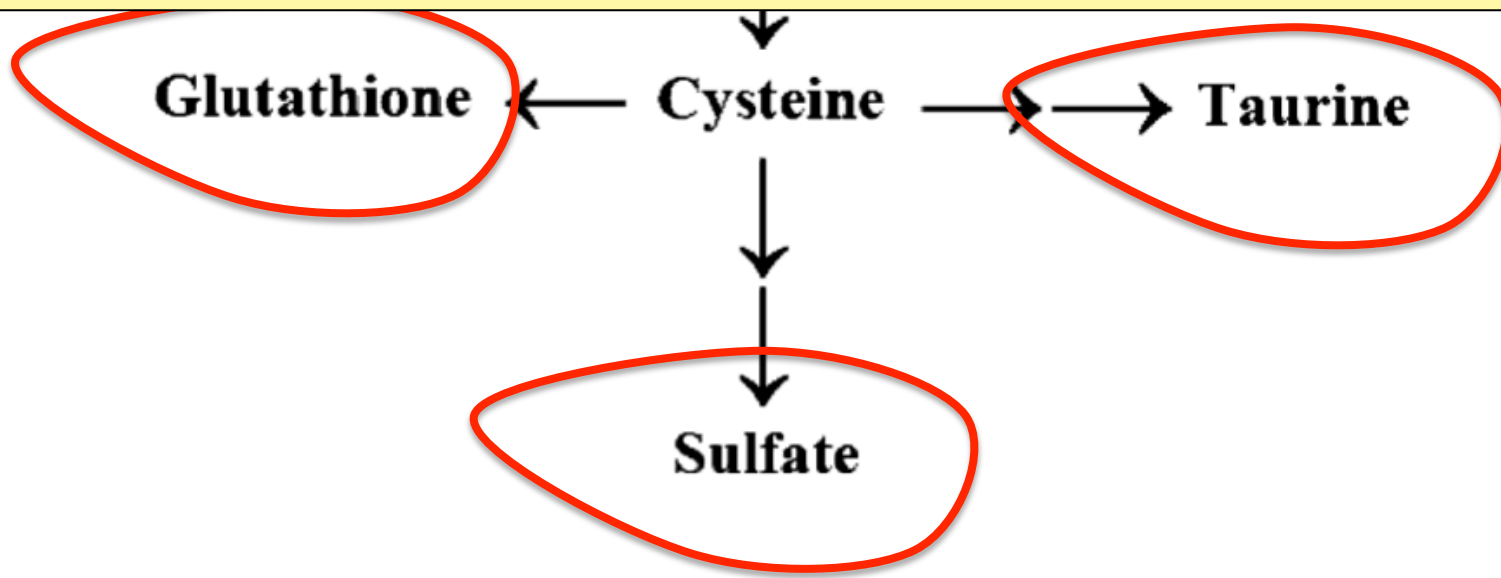


\*Figure 1, DA Geier et al., Neurochem Res (2009) 34:386–393.

# Transsulfuration Pathway\*

Homocysteine

Three very important molecules!!!



\*Figure 1, DA Geier et al., Neurochem Res (2009) 34:386–393.

# Recapitulation

- The timing of mandatory folic acid enrichment is uncanny: hide pending epidemic in spina bifida?
- Folic acid is synthetic, and it leads to excessive oxidation in the liver and/or depleted  $\text{BH}_4$
- Folate trap leads to redirection of homocysteine towards sulfate to detox xenobiotics
- An excess of unmetabolized folic acid paradoxically leads to cerebral folate deficiency
- More generally, too many vitamins (and drugs!) can deplete the supply of sulfur-containing metabolites

# Evidence of Harm

# Early Infant Exposure to Excess Multivitamin: A Risk Factor for Autism?\*

- High multivitamin feeding is very common in early infancy
- Excess vitamins may cause neurotoxicity and disturb monoamine-neurotransmitter metabolism by depleting the body's methyl-groups and sulfate pools
- Autism is often associated with abnormal levels of monoamine neurotransmitters

\*S-S Zhou et al., Autism Research and Treatment Volume 2013, Article ID 963697

# “High folic acid consumption leads to pseudo-MTHFR deficiency, altered lipid metabolism, and liver injury in mice”\*

- Fed mice excessive amounts of folic acid
- *Reduced* methylation capacity in liver
- CYP7A1 level was dramatically reduced. (rate limiting enzyme in bile acid synthesis)
- Caused liver damage and fatty liver disease



Works synergistically with glyphosate to disrupt bile flow

\*KE Christensen et al., Am J Clin Nutr 2015;101:646–58.

# **Folic Acid Supplements in Late Pregnancy increase Risk to Asthma in Children \***

- Prospective cohort of Australian families
- Folic acid supplements in late pregnancy increases risk of asthma in children at 3.5 and 5.5 years
- Supports possible role of folate-impaired methylation in altering fetal immune phenotype towards Th2

\*MJ Whitrow et al., American Journal of Epidemiology 2009;170:1486–1493

# Folic Acid and Autism Risk\*

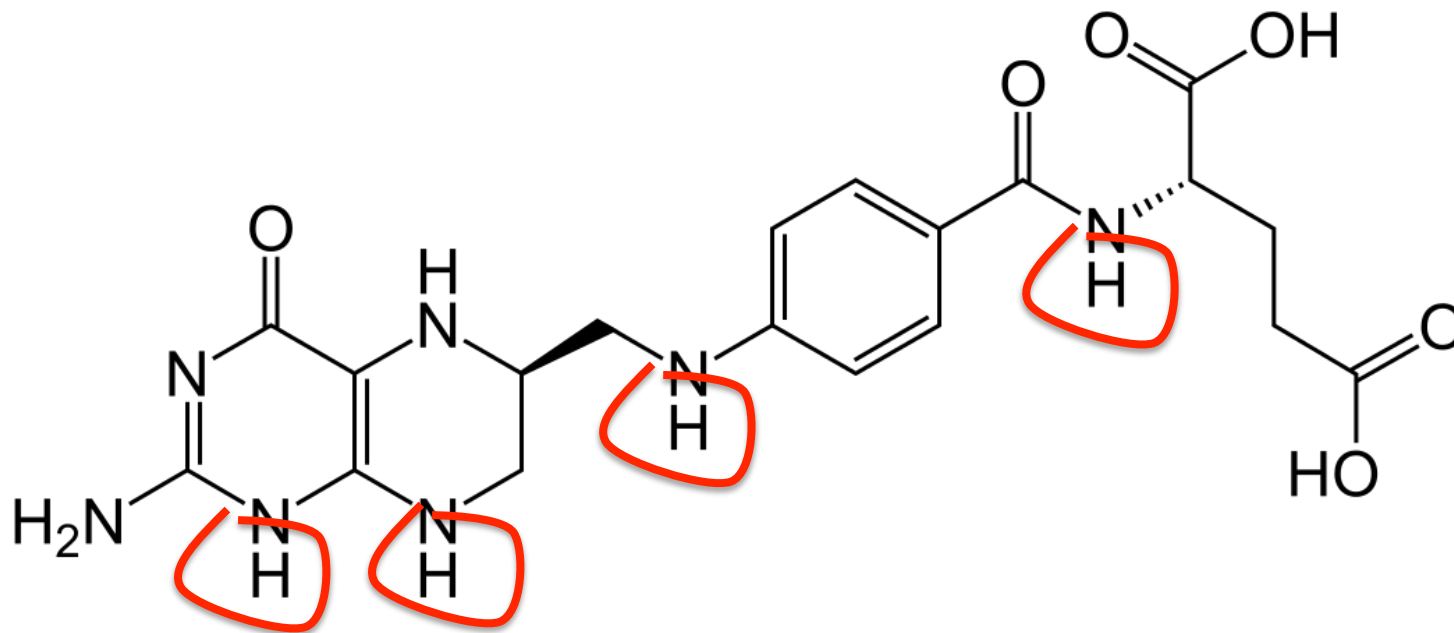
- Effects of ubiquitous synthetic supplementation of vitamins is unpredictable
  - Blanket approach may harm those with specific gene variants
- Folic acid supplementation during gestation is associated with an increased risk for autism.
- Unexpected increases in asthma and breathing problems associated with folic acid use
- Excess methylation during gestation leads to epigenetic changes?
- Folic acid supplements during gestation linked to premature birth and low birth weight

\*MC DeSoto and RT Hitlan, Journal of Pediatric Biochemistry 2 (2012) 251–261



# “Cerebral folate deficiency with developmental delay, autism, and response to folinic acid”\*

Fol<sup>in</sup>ic acid is a form of TETRAHYDRO-folate

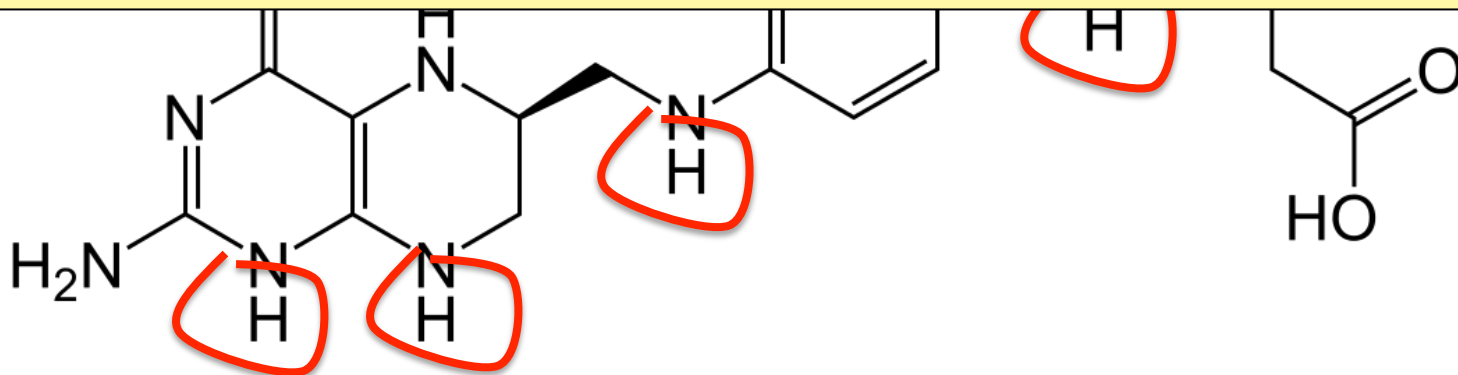


\* P Moretti et al., *Neurology* March 22, 2005 vol. 64 no. 6 1088-1090

# “Cerebral folate deficiency with developmental delay, autism, and response to folinic acid”\*

Fol<sup>in</sup>ic acid is a form of TETRAHYDRO-folate

Folate receptor antibodies due to excess folic acid in the blood???



\* P Moretti et al., *Neurology* March 22, 2005 vol. 64 no. 6 1088-1090

# Folic Acid Worsens Cerebral Folate Deficiency\*

- Cerebral folate deficiency is a condition where cerebral spinal fluid concentrations of 5-methyltetrahydrofolate (5MTHF) are anomalously low despite adequate levels in the blood
- Symptoms appear beginning at 4 months of age
  - Irritability and sleep disturbances →
  - Slowed head growth, visual disturbances, hearing loss
- Treatment is oral administering of folinic acid.
- Folic acid supplements worsen the condition

\* Hyland et al., J Inherit Metab Dis. 2010 Oct;33(5):563-70.

# “Cerebral Folate Deficiency in Autism Spectrum Disorders”\*

- Folinic acid has an excellent safety record and has been shown to normalize cerebrospinal levels of 5MTHF in children with autism.
- “As folic acid (the inactive, oxidized form of folate) can compete for the binding site on FR1, it is probably wise to discontinue the use of folic acid-containing supplements.”

\*R Frye and D. Rossignol. Autism Science Digest Issue 2: 9-15.

# Folic Acid Increases Cancer Risk?\*

- 6261 Patients in Norway with ischemic heart disease
- (no folic acid fortification in flour)
- Treatment with 0.8 mg/d of folic acid from 1998 to 2005
- Results:
  - Serum folate increased six-fold in treatment group
  - 10% of treatment group and only 8.4% of controls developed cancer
  - 4% of treatment group died from cancer, and only 2.9% of controls.
  - 16.1% of treatment group died of any cause and only 13.8% of controls.
- Hypothesis: folic acid enhances DNA replication and neoplastic growth

\*M Ebbing et al., JAMA 2009 302(19) 2119-2126

# Increased cancer cell proliferation in prostate cancer patients with high levels of serum folate \*

- Folic acid supplementation is associated with increased risk to prostate cancer
- 40% of patients were taking folic acid supplements
- Serum levels in top quartile were 6-fold above adequate levels
  - Nearly half of them did not take supplements
- Serum folate levels correlate with tumor folate levels and with tumor growth

\* JJ Tomaszewski et al., Prostate. 2011; 71(12): 1287–1293.

# Prospective Danish Cohort Study\*

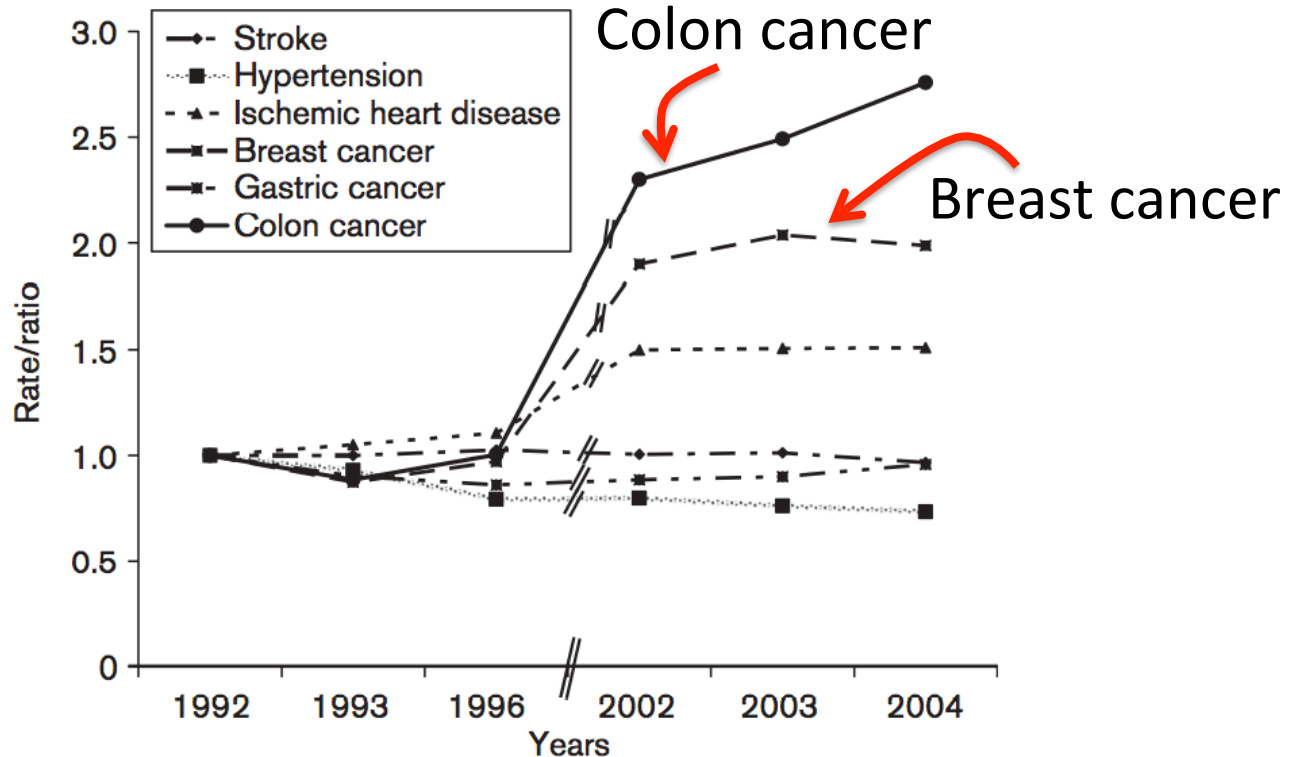
"supplemental folic acid was associated with a significantly increased mortality, whereas no other micronutrient supplement was associated with mortality."

- 55,453 middle-aged Danes
- Others have found increased risk to colorectal adenomas, prostate cancer, lung cancer, and mortality.

\* N Roswall et al, Nutrition Research 2012; 56:5466.

# Folic Acid and Colon Cancer in Chile\*

Mandatory folic acid supplementation introduced in 2000

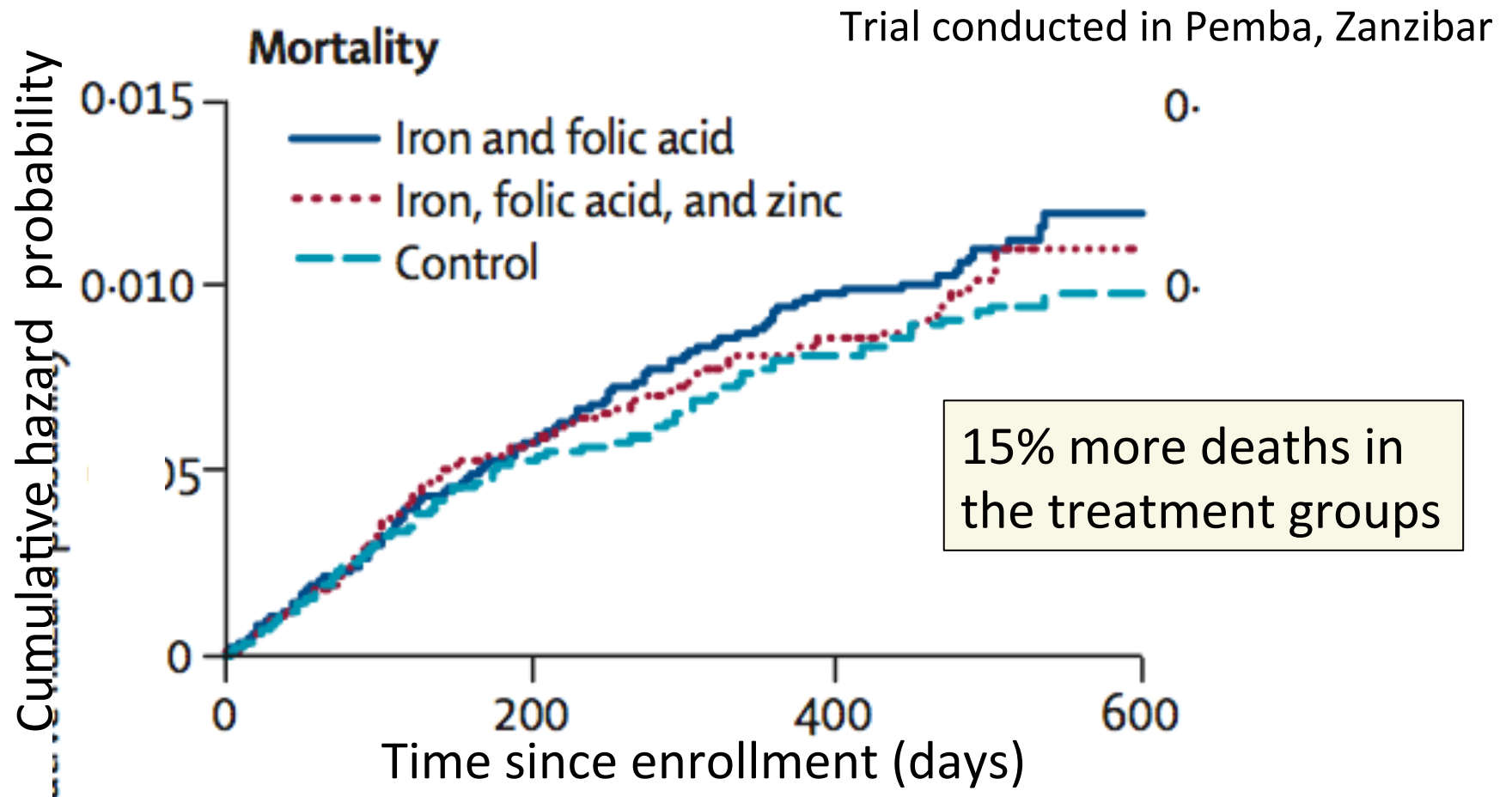


Rate/ratio of hospital discharge because of colon cancer in adults aged 45–64 years, before and after the start of the mandatory flour fortification program with 220 µg of synthetic folic acid/100 g of wheat flour. Rate /ratios are expressed as the rate for each year/the rate for 1992.

\*S Hirsch et al., Eur J Gastroenterol Hepatol. 2009;21(4):436-9.



# Folic Acid Supplement Trial in Africa: Failed!\*



\*S Sazawal et al., The Lancet Jan 14, 2006; 367:133-143.

# Interaction with Minerals

# Folic Acid and Zinc\*

- Folic acid forms insoluble chelate with zinc in the gut and prevents absorption

“The findings from this study raise questions about the significance of self-medication with folic acid and the inclusion of folic acid in prenatal vitamin preparations for zinc nutriture.”

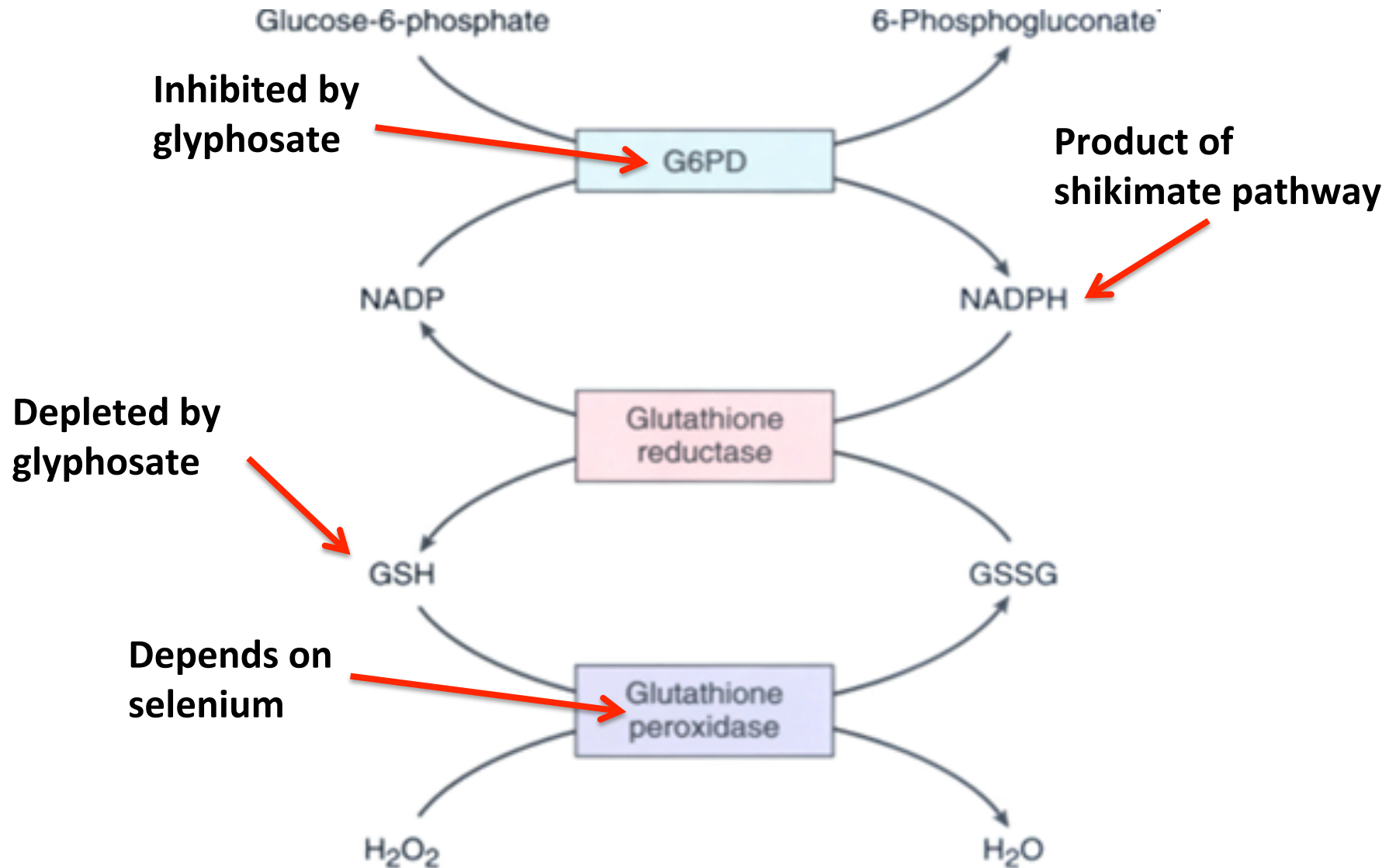
\*DB Milne et al., *The American Journal of Clinical Nutrition* 39: 1984, **535-539**.

# “Iron-Fortified vs Low-Iron Infant Formula” \*

- Children who received 12.7 mg/L of iron-fortified formula as infants had *lower* cognitive and visual-motor scores at 10 years than those receiving low-iron formula
- “Iron is an essential nutrient of which both too little and too much are problematic. If unneeded iron were absorbed, the brain might be vulnerable to adverse effects of excess iron.”

\*B Lozoff et al. Arch Pediatr Adolesc Med 166(3), 208-215, 2012.

# This Detoxification Scheme is Essential in Red Blood Cells



# This Detoxification Scheme is Essential in Red Blood Cells

Glucose-6-phosphate

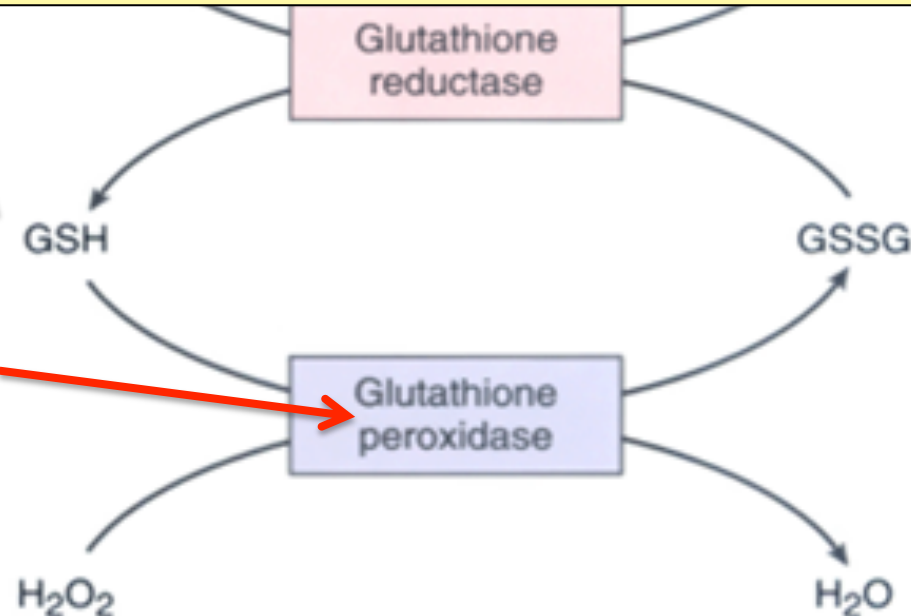
6-Phosphogluconate

Inhibited by

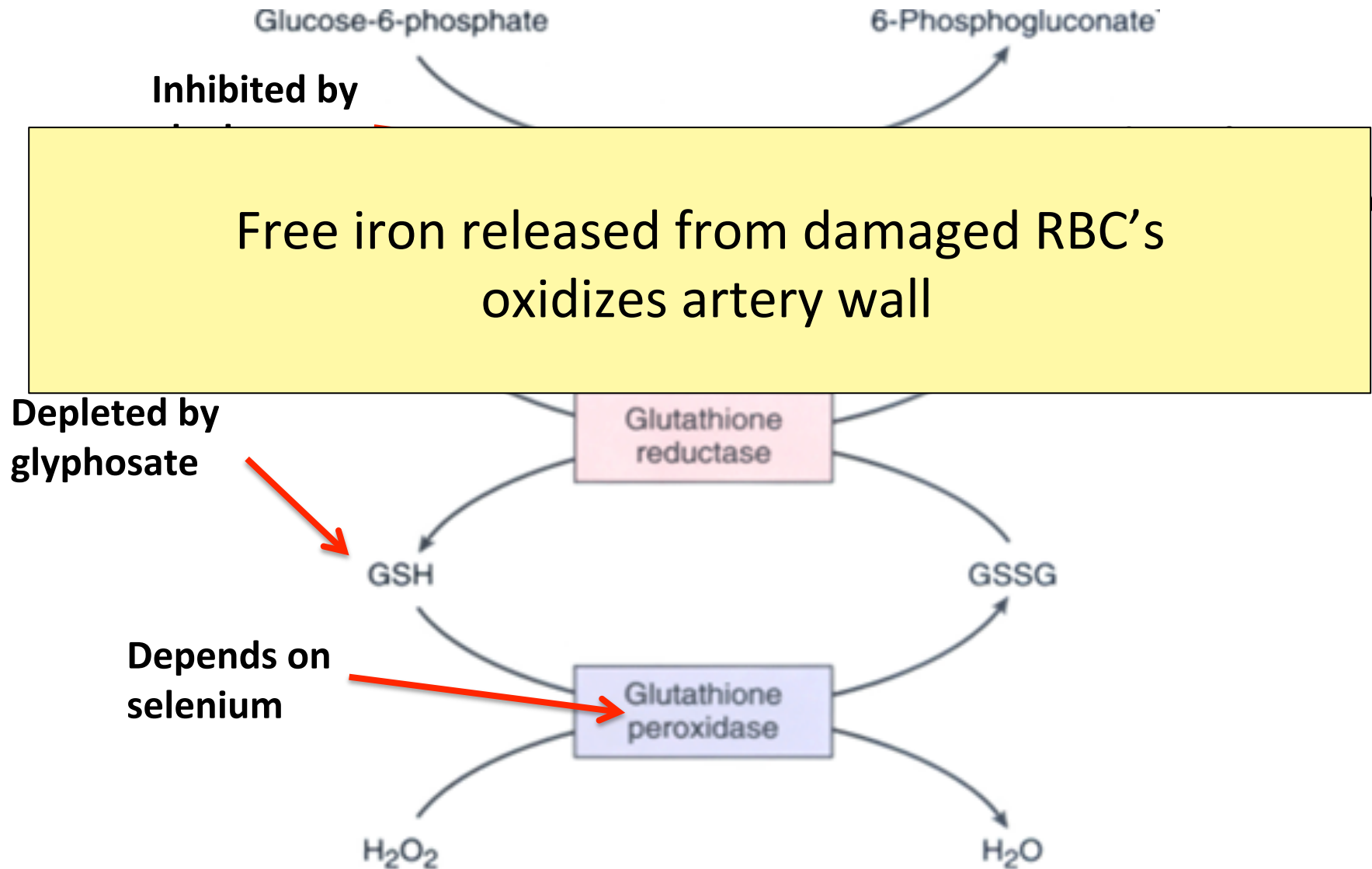
G6PD Deficiency Leads to Hemolysis and Anemia

Depleted by  
glyphosate

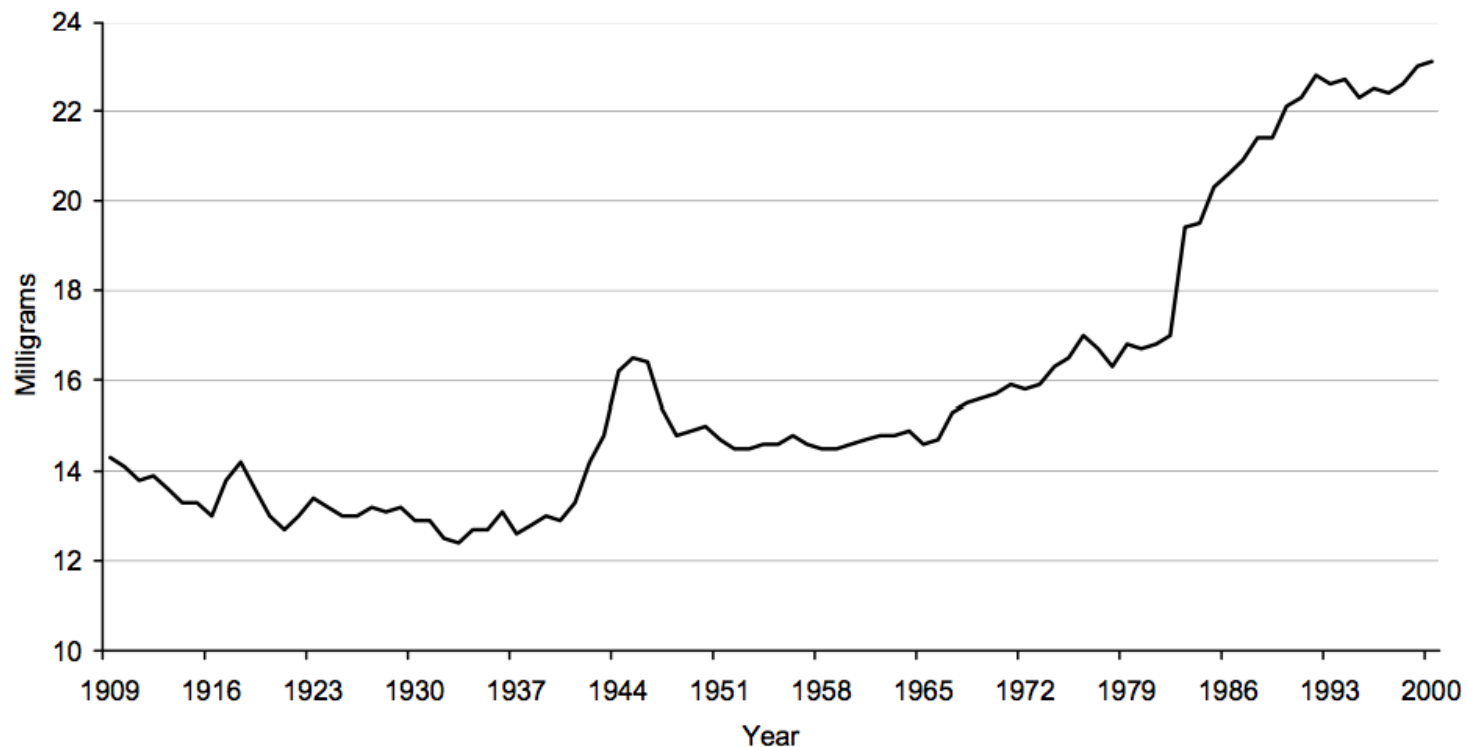
Depends on  
selenium



# This Detoxification Scheme is Essential in Red Blood Cells



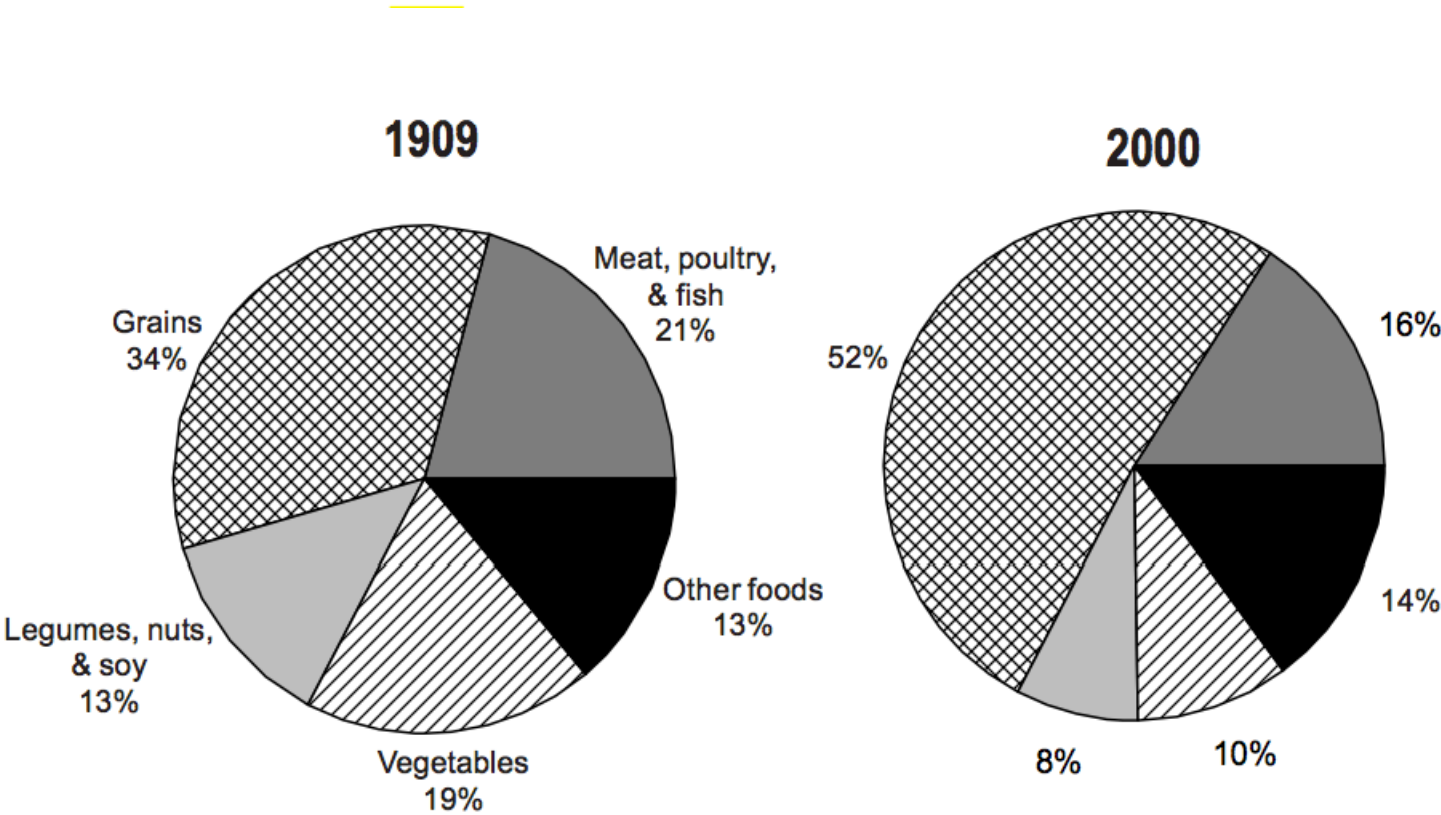
# Iron in the US Food Supply: per capita per day, 1909-2000\*



\*Source: Figure 41, USDA Nutrient Content of the U.S. Food Supply, 1909-2000



# Sources of Iron in the US Food Supply\*



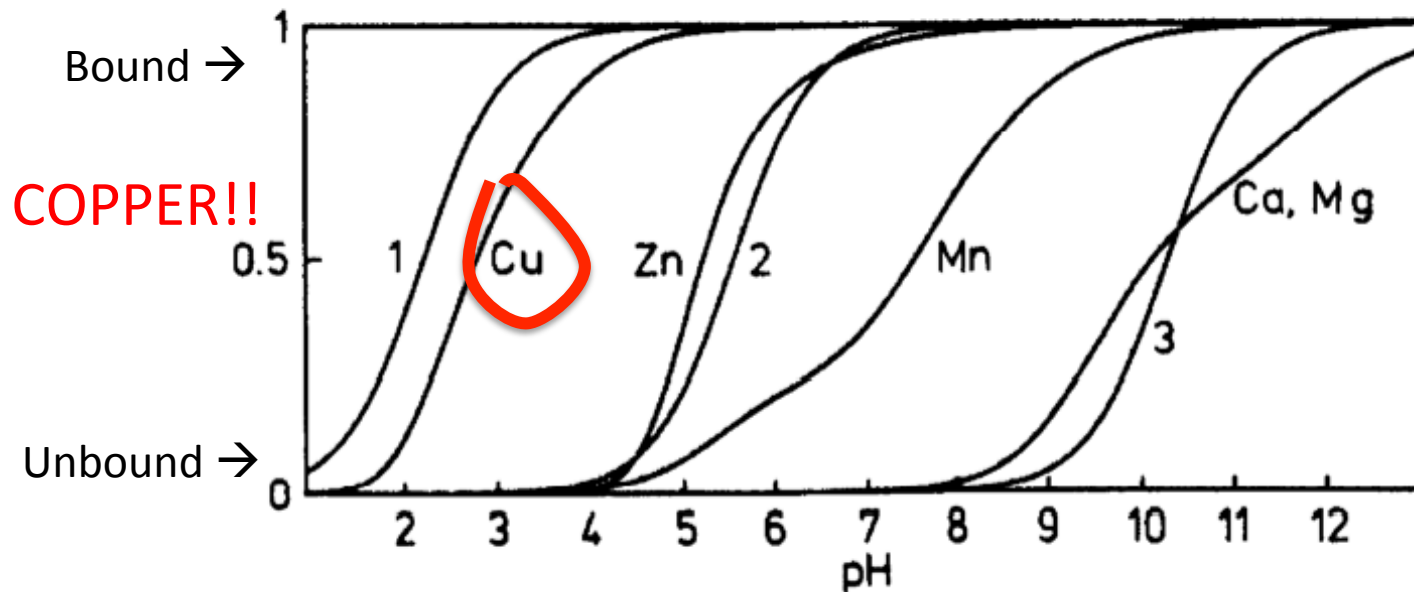
\*Source: Figure 42, USDA Nutrient Content of the U.S. Food Supply, 1909-2000

# A Role for Copper Deficiency\*

- Copper catalyzes methionine synthase → elevated homocysteine with copper deficiency
- Copper catalyzes superoxide dismutase, an antioxidant
- PON-1, another antioxidant, breaks down homocysteine: it depends on copper too!
- Homocysteine thiolactone suppresses lysyl oxidase, an enzyme that maintains healthy artery walls
- Result: arterial damage and heart disease!

\*LM Klevay, Cellular and Molecular Biology 2006;52(5):11-15.

# Glyphosate Binding to Metals\*

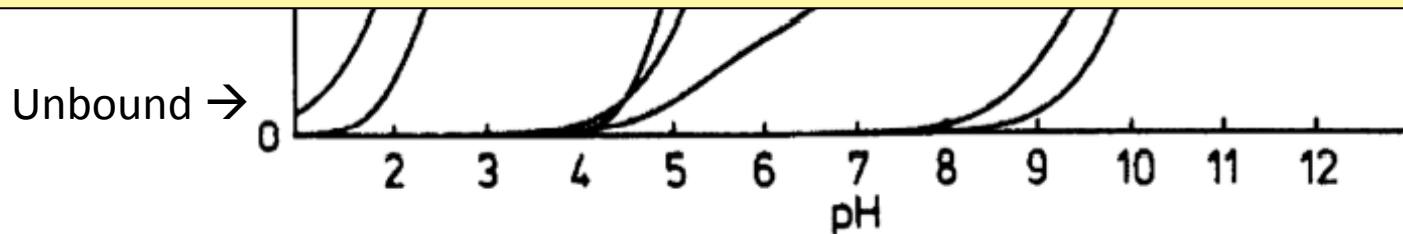


**Fig. 2.** Fractions of metal complexed as functions of pH at  $C_M = C_L = 0.0025$  M and  $I = 0.1$  ( $KNO_3$ ). The curves marked 1, 2, and 3 represent the base fractions at the three dissociation steps of glyphosate.

Plot provided by Frank Dean, personal communication

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# Recapitulation: Effects of Glyphosate

- Glyphosate preferentially kills microbes in the gut that synthesize folate
  - Folate synthesis requires the pathway that glyphosate disrupts
- Glyphosate damages red blood cells, causing release of free iron, which is toxic, while also causing anemia
- Glyphosate chelates copper making it unavailable
- Glyphosate induces excess retinoic acid leading to neural tube defects
- Glyphosate causes oxidative damage in the liver, working synergistically with supplemental folic acid
  - Depletes the supply of NADPH and glutathione

# “Neurobehavioural effects of developmental toxicity”\*

“Our very great concern is that children worldwide are being exposed to unrecognised toxic chemicals that are silently eroding intelligence, disrupting behaviours, truncating future achievements, and damaging societies, perhaps most seriously in developing countries.

*A new framework of action is needed.”\**

\*P Grandjean and PJ Landrigan. The Lancet March 2014; 13: 330-338

**What You Can Do**

# Eat Organic Whole Foods





# Eat Foods that Contain Folate



# Avoid Foods Fortified with

And campaign for removing legislation that requires fortification!



**Don't Use Roundup in your Yard!!**



# Summary

- Glyphosate likely plays a role in spina bifida
- Folic acid fortification of wheat-based products is most likely a big mistake
- Folic acid is a synthetic form of folate that causes oxidative damage in the liver, depletes antioxidants, and can lead to cerebral folate deficiency
  - Linked to autism and cancer, among others
- Iron supplements are likely also causing harm
- Eating an organic diet that is rich in folate is the best way to protect from folate deficiency