Glyphosate's disruption of methylation/transsulfuration pathways as a key factor in autism and other diseases

Stephanie Seneff, MIT CSAIL

Methylation Summit

July 15, 2018

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Outline

- Introduction
- Glyphosate and Folic Acid Fortification
- Cholesterol Sulfate and Heparan Sulfate
- Methylation and Transsulfuration Pathways
- Glyphosate Displacing Glycine during Protein Synthesis
- How Glyphosate Disrupts Methylation and Sulfation
- Summary

Introduction

Roundup and GMO Crops

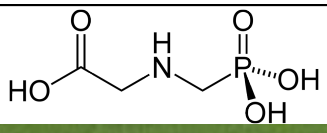
What is glyphosate?

Roundup and GMO Crops

Roundup and GMO Crops

GMO Roundup-Ready corn, soy, canola, sugar beets cotton, tobacco and alfalfa

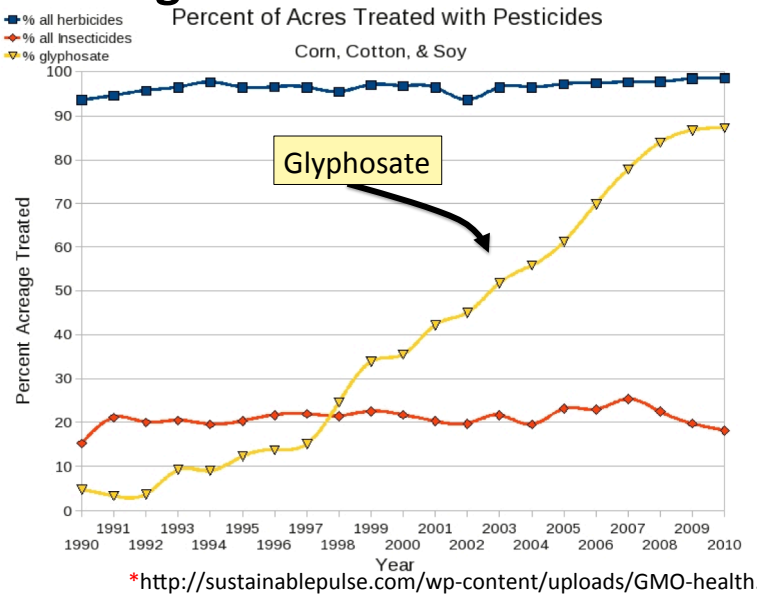
Roundup as a Desiccant/Ripener just before Harvest



Glyphosate!!

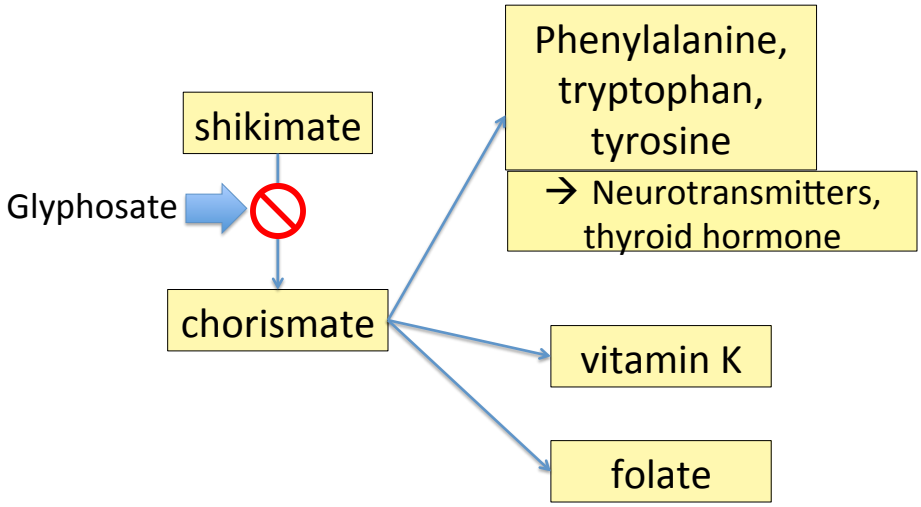
- Glyphosate is now the #1 herbicide in use in the U.S. and is increasingly used around the world
  - Developed and patented by Monsanto in the 1970's
  - Introduced into the US food chain in 1974
  - Came out from under patent in 2000
  - Inhibits an enzyme in the *shikimate* pathway involved in the synthesis of tyrosine, tryptophan and phenylalanine (the three *aromatic amino acids*)
- Huge expansion of GMO corn, soy, cotton and canola crops has led to sharp increases in the last two decades

Glyphosate vs. Other Pesticides: Usage in the United States*



*http://sustainablepulse.com/wp-content/uploads/GMO-health.pdf

Shikimate Pathway Disruption

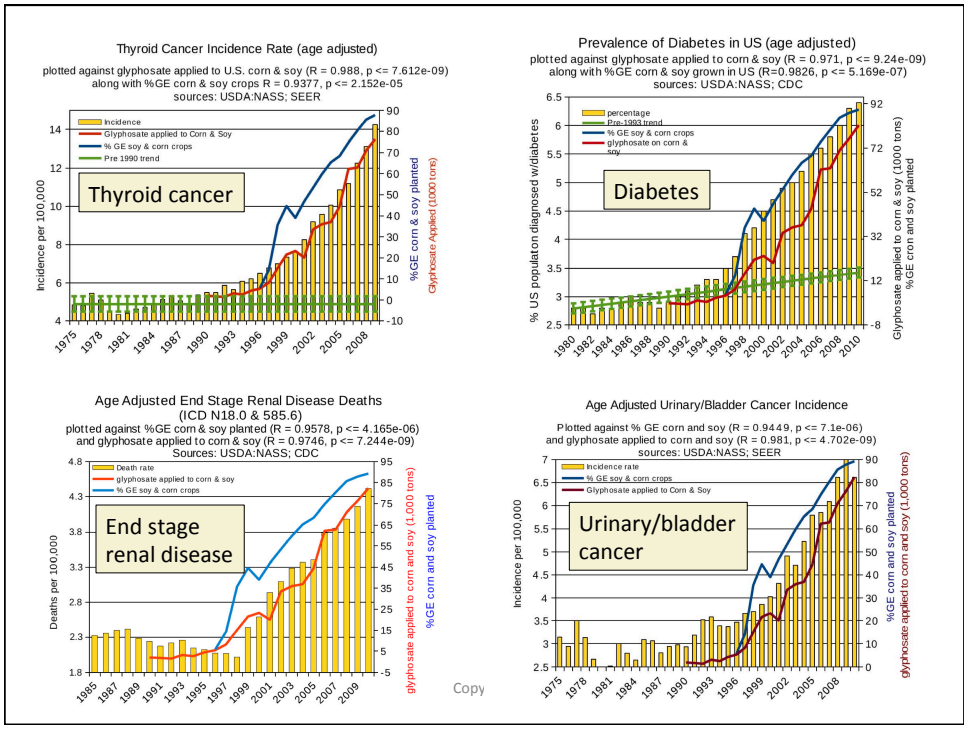


Paper Showing Strong Correlations between Glyphosate Usage and Chronic Disease

Journal of Organic Systems, 9(2), 2014 ORIGINAL PAPER

Genetically engineered crops, glyphosate and the deterioration of health in the United States of America

Nancy L. Swanson[1], Andre Leu[2]*, Jon Abrahamson[3] and Bradley Wallet[4]
[1] *Abacus Enterprises, Lummi Island, WA, USA*
[2] *International Federation of Organic Agricultural Movements, Bonn, Germany*
[3] *Abacus Enterprises, Lummi Island, WA, USA*
[4] *Crustal Imaging Facility, Conoco Phillips School of Geology and Geophysics, University of Oklahoma, USA*
* *Corresponding author: andreleu.al@gmail.com*


Thyroid Cancer Incidence Rate (age adjusted)
plotted against glyphosate applied to U.S. corn & soy (R = 0.988, p <= 7.612e-09)
along with %GE corn & soy crops R = 0.9377, p <= 2.152e-05
sources: USDA:NASS; SEER
Incidence
Glyphosate applied to Corn & Soy
% GE soy & corn crops
Pre 1990 trend
Thyroid cancer
Incidence per 100,000
%GE corn & soy planted
Glyphosate Applied (1000 tons)
Prevalence of Diabetes in US (age adjusted)
plotted against glyphosate applied to corn & soy (R = 0.971, p <= 9.24e-09)
along with %GE corn & soy grown in US (R=0.9826, p <= 5.169e-07)
sources: USDA:NASS; CDC
percentage
Pre-1993 trend
% GE soy & corn crops
glyphosate on corn & soy
Diabetes
% US population diagnosed w/diabetes
Glyphosate applied to corn & soy (1000 tons)
%GE cron and soy planted
Age Adjusted End Stage Renal Disease Deaths
(ICD N18.0 & 585.6)
plotted against %GE corn & soy planted (R = 0.9578, p <= 4.165e-06)
and glyphosate applied to corn & soy (R = 0.9746, p <= 7.244e-09)
Sources: USDA:NASS; CDC
Death rate
glyphosate applied to corn & soy
% GE soy & corn crops
End stage
renal disease
Deaths per 100,000
glyphosate applied to corn and soy (1,000 tons)
%GE corn and soy planted
Age Adjusted Urinary/Bladder Cancer Incidence
Plotted against % GE corn and soy (R = 0.9449, p <= 7.1e-06)
and glyphosate applied to corn and soy (R = 0.981, p <= 4.702e-09)
sources: USDA:NASS; SEER
Incidence rate
% GE soy & corn crops
Glyphosate applied to Corn & Soy
Urinary/bladder
cancer
Incidence per 100,000
%GE corn and soy planted
glyphosate applied to corn and soy (1,000 tons)
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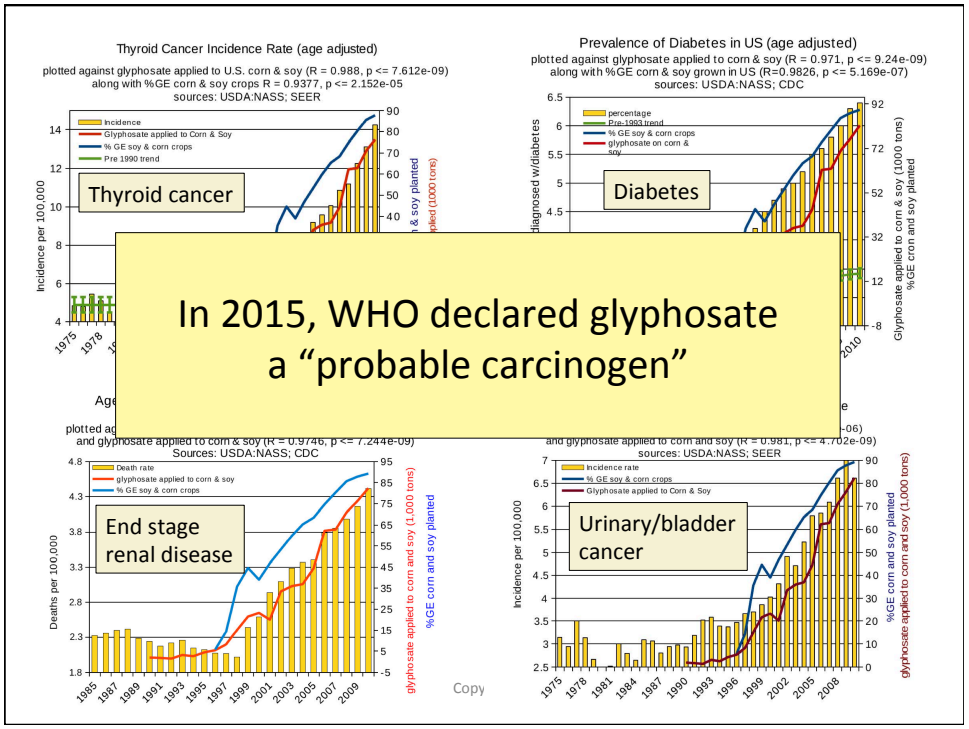
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sources: USDA:NASS; CDC
Diabetes
In 2015, WHO declared glyphosate
a “probable carcinogen”
End stage
renal disease
Urinary/bladder
cancer
Copy

Quote from the Conclusion*

"Although correlation does not necessarily mean causation, when correlation coefficients of over 0.95 (with *p*-value significance levels less than 0.00001) are calculated for a list of diseases that can be directly linked to glyphosate, via its known biological effects, it would be imprudent not to consider causation as a plausible explanation."

*NL Swanson et al. Journal of Organic Systems 9(2), 2014, p. 32,

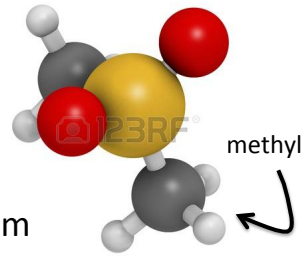
Glyphosate and Folic Acid Fortification

The Big Picture

- Glyphosate disrupts folate synthesis by gut microbes (from shikimate pathway)
- U.S. mandated folic acid fortification in 1998, simultaneous with the widespread introduction of Roundup-Ready crops
- Folic acid is an oxidized, unmethylated form of methyl-tetrahydrofolate (5-MTHF)
  - It costs the liver dearly to "fix" it
- Excess serum folic acid leads to cerebral folate deficiency due to folic acid binding to brain receptors
  - This is a risk factor for autism

Folate and Methylation Pathways*

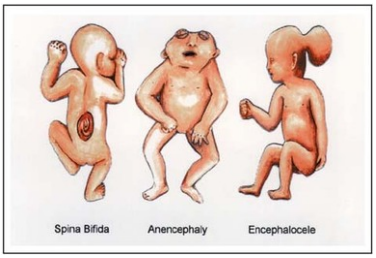
- Folate donates a methyl group for numerous biochemical pathways
  - Neurotransmitter synthesis
  - DNA biosynthesis
  - Regulation of gene expression
  - Amino acid synthesis and metabolism
  - Myelin synthesis and repair
- 5-MTHF impacts mood and cognition via control of neurotransmitter synthesis



*AL Miller. Alternative Medicine Review 2008; 13(3): 216-226

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



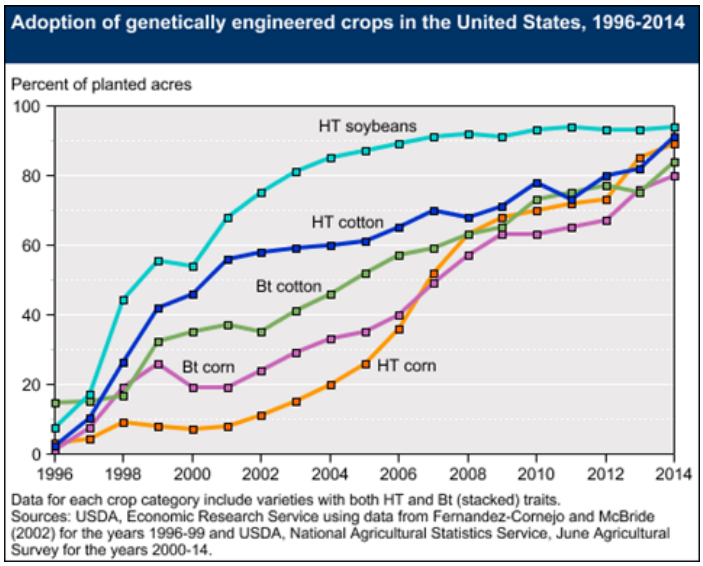
Serum Folate Decreased in Women Aged 15-54 after Folic Acid Fortification was Introduced! *

- Serum folate decreased in women of reproductive age among Caucasians, Blacks and Hispanics
- GMO Roundup-Ready crops were dramatically ramping up at the same time

Years	Serum Folate (Caucasians)
1999-2000	13.4
2001-2002	12.1
2003-2004	11.3

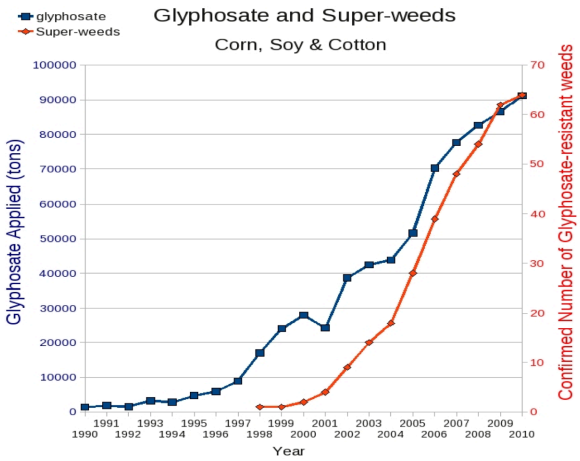
*Centers for Disease Control and Prevention. MMWR Morb Mortal Wkly Rep 2007;55:1377-80.

Adoption of GM Crops in U.S.



HT = herbicide (glyphosate) tolerant

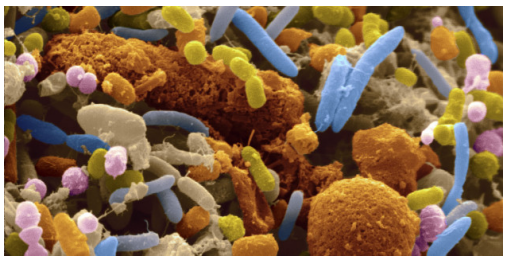
Glyphosate and Superweeds: U.S.*



*http://sustainablepulse.com/wp-content/uploads/GMO-health.pdf

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."



*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
- d

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.

"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 e tal., Am J Clin Nutr 2015;101:646–58.

Assessment of Folic Acid Supplementation in Mice*

"Contrary to expectations, we find that three genetic mutants respond adversely to FA [folic acid] supplementation with increased incidence of NTDs [neural tube defects] in homozygous mutants, occurrence of NTDs in heterozygous embryos and embryonic lethality prior to NT closure."

*A Marean et al., Human Molecular Genetics 2011; 20(18): 3678-3683.

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

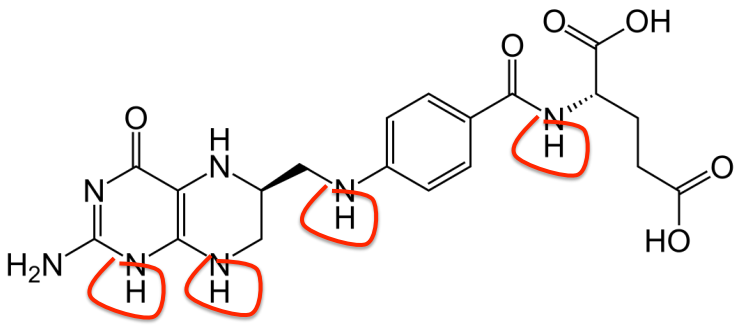
Folic Acid and Autism Risk*

- 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*in*ic acid is a form of TETRAHYDRO-folate

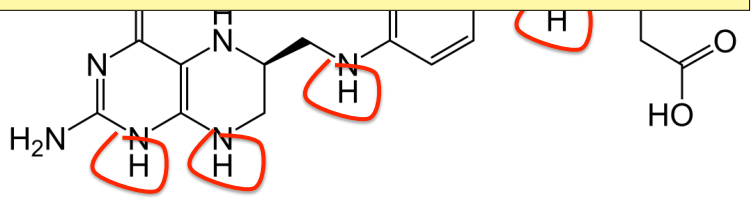


* *P Moretti et al., Neurology March 22, 2005 vol. 64 no. 6 1088-1090*

"Cerebral folate deficiency with developmental delay, autism, and response to folinic acid"*

Fol*in*ic acid is a form of TETRAHYDRO-folate

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



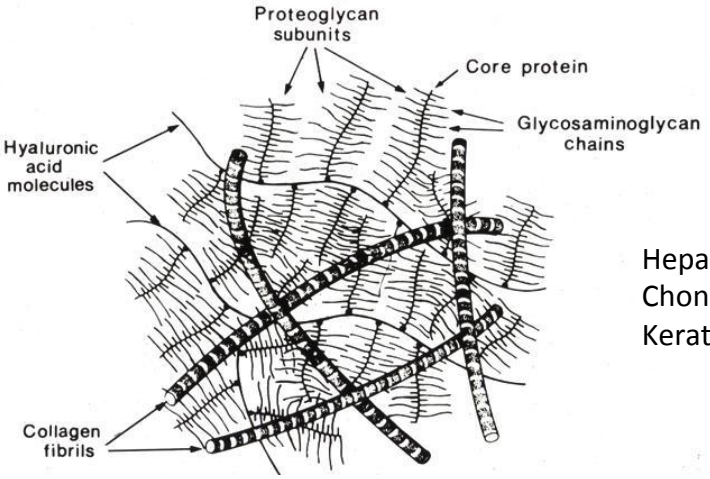
* *P Moretti et al., Neurology March 22, 2005 vol. 64 no. 6 1088-1090*

Cholesterol Sulfate And Heparan Sulfate

The Big Picture

- Connective tissues contain lots of sulfate
- Fetus depends on mother to provide sulfate
- Sulfate is severely deficient in autism
- Cholesterol supply to fetus depends on sulfate
  - Cholesterol sulfate normally accumulates in high amounts in the placental villi during third trimester
  - Cholesterol deficiency leads to projectile vomiting due to pyloric stenosis
- Sulfate is essential for clearing cellular debris
- Low sulfate leads to high oxalate with many symptoms

Connective Tissue Contains Lots of Sulfate



Heparan sulfate
Chondroitin sulfate
Keratan sulfate

Sulfate in Fetal Development*

- Fetus depends on mother for sulfate supply
- Sulfate is essential for transporting sterols (like estrogen and DHEA) and supplying extracellular matrix proteins everywhere with sufficient negative charge
- Sulfate detoxifies xenobiotics like acetaminophen (Tylenol) and is essential for excreting toxins like aluminum and mercury
- Sulfate is severely deficient in autistic children (1/3 the normal level of free sulfate in blood stream)

* PA Dawson. Semin Cell Dev Biol 2011 Aug;22(6):653-9.

Heparan Sulfate Proteoglycans*

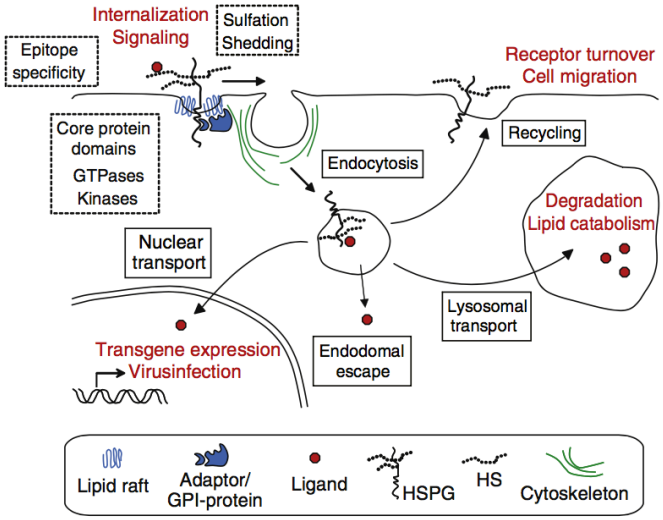


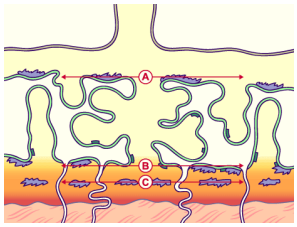
*Figure 2 in HC Christianson et al., Matrix Biology 2014;35: 51-55

Heparan Sulfate Deficiency and Autism*

- Experiment with "designer" mice: impaired heparan sulfate synthesis in brain
- Mice exhibited all the classic features of autism – both cognitive and social

* F. Irie et al., Autism-like socio-communicative deficits and stereotypies in mice lacking heparan sulfate. PNAS Mar. 27, 2012, 109(13), 5052-5056.

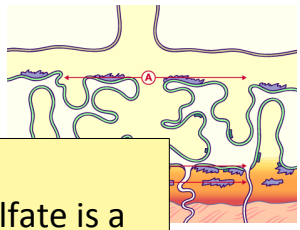
Cholesterol Sulfate in Placental Villi*



- Placental villi are highly enriched in cholesterol sulfate, especially in third trimester of pregnancy
- Mother's serum cholesterol sulfate steadily rises through pregnancy
- In third trimester, villi contain 24 picomol/mg of cholesterol sulfate, compared to only 1.5 in blood serum of a non-pregnant woman

*B Lin et al. J. Chromatogr. B. Biomed. Sci. Appl. 1997, 704, 99–104.

Cholesterol Sulfate in Placental Villi*

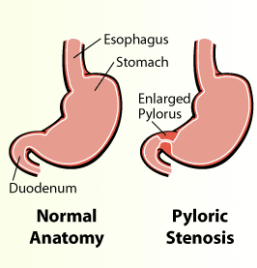


- Placental villi are highly enriched in cholesterol sulf… trim…
- Mo… …adily rise…
- In t… …ol/mg of cholesterol sulfate, compared to only 1.5 in blood serum of a non-pregnant woman

Hypothesis: cholesterol sulfate is a major supplier of both cholesterol and sulfate to the fetus

*B Lin et al. J. Chromatogr. B. Biomed. Sci. Appl. 1997, 704, 99–104.

Pyloric Stenosis and Autism



- Affects 2 out of 1000 births
  - Pyloric valve at base of stomach is enlarged, constricting flow
  - Severe projectile vomiting and dehydration, with electrolyte imbalance.
  - Corrective surgery is often required
- Pyloric stenosis is associated with low serum cholesterol*
- Autism is associated with increased risk to pyloric stenosis**

*Feenstra B, et al. JAMA 2013; 310(7): 714-721.
**M.L. Wier et al., Med Child Neurol 2006;48(6):500-507.

Low Sulfate, High Oxalate Phenotype*

- Gut Dysbiosis
  - Decreased sulfomucins, colitis, IBD, leaky gut
  - Increased susceptibility to pathogens
- Fatty liver disease
  - Reduced detox of heavy metals and toxic chemicals
  - Elevated serum LDL
- Decreased insulin function
- Adrenal insufficiency
- Increased cancer risk
- Stunted growth, slow metabolism
- Serotonin deficiency in brain
- Autism linked to sulfate wasting in kidneys

*Dr. Rostenberg
www.beyondmthfr.com/side-high-oxalates-problems-sulfate-b6-gut-methylation

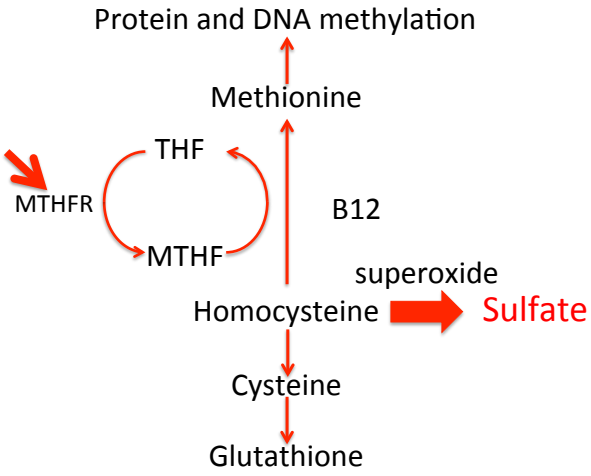
Methylation and Transsulfuration Pathways

The Big Picture

- Methionine is an essential sulfur-containing amino acid produced by gut microbes and disrupted by glyphosate
- Methionine sits at the crossroads of the methylation and trans-sulfuration pathways
- Both methylation and sulfation are essential for development and neuronal function
- Glyphosate also suppresses the supply of the B vitamin, folate, essential for methyl transfer

Methionine and Cysteine

MTHFR gene variants linked to autism*



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

Generating Methionine from Homocysteine

Methionine ← *Methionine synthase* ← Homocysteine

Requirements:
Working MTHFR enzyme
Cobalamin (vitamin B12)
Zinc
Vitamin B6
Methyl tetrahydro***folate***

Generating Methionine from Homocysteine

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

Methionine

Methionine synthase

Homocysteine

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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 tetrahydro***folate***

Transsulfuration Pathway*

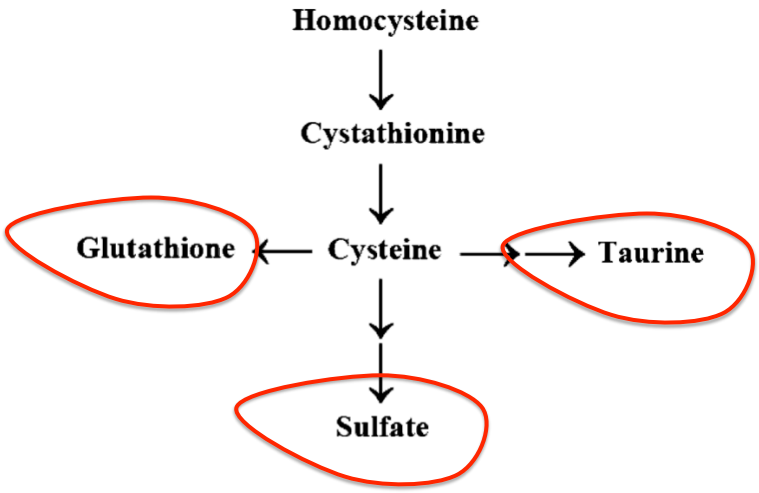
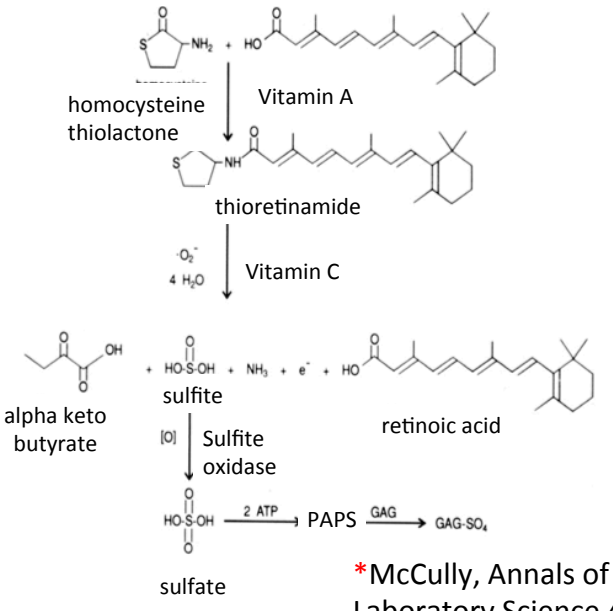


*Figure 1, DA Geier et al., Neurochem Res (2009) 34:386–393.

Pathway from Homocysteine to Sulfate*



*McCully, Annals of Clinical and Laboratory Science 41:4, 300-313, 2011

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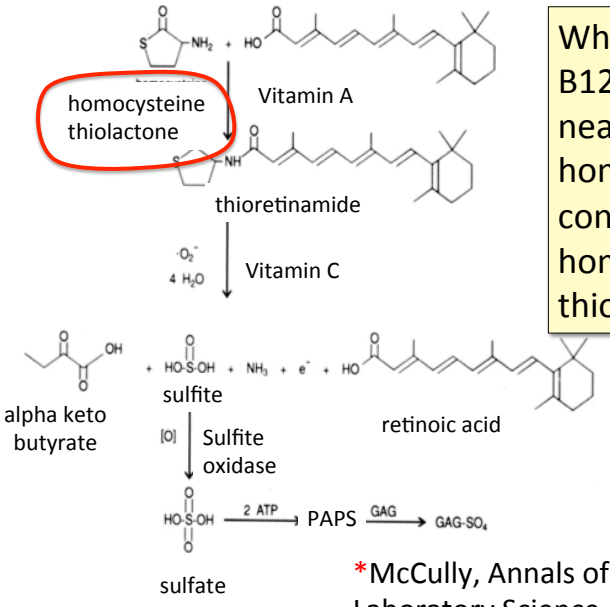

When folate and B12 are deficient, nearly all homocysteine is converted to homocysteine thiolactone

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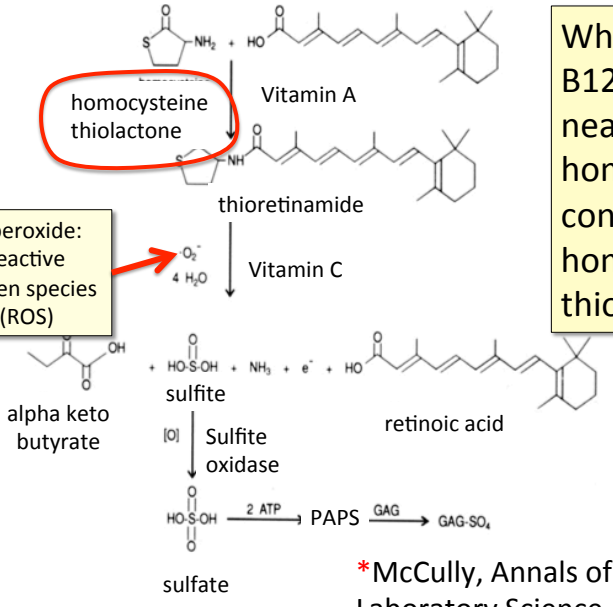

Superoxide: Reactive oxygen species (ROS)

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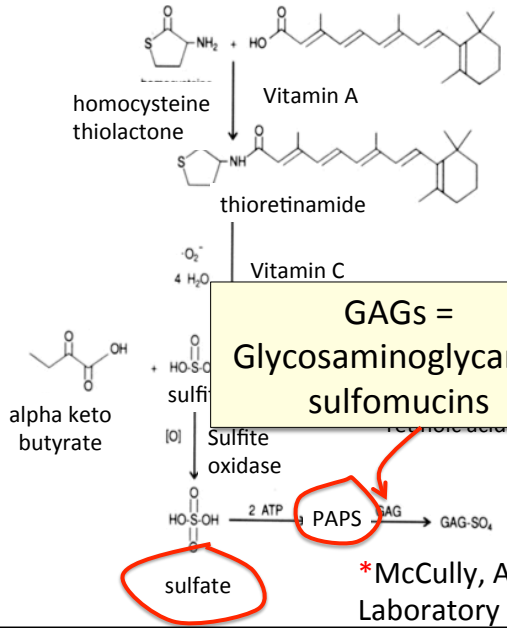
Pathway from Homocysteine to Sulfate*



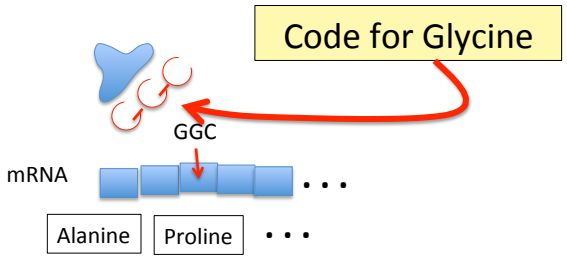
When folate and B12 are deficient, nearly all homocysteine is converted to homocysteine thiolactone

GAGs = Glycosaminoglycans = sulfomucins

*McCully, Annals of Clinical and Laboratory Science 41:4, 300-313, 2011

Glyphosate Displacing Glycine in Protein Synthesis

What If Glyphosate Could Insert Itself Into Protein Synthesis???



-- Any proteins with conserved glycine residues are likely to be affected in a major way

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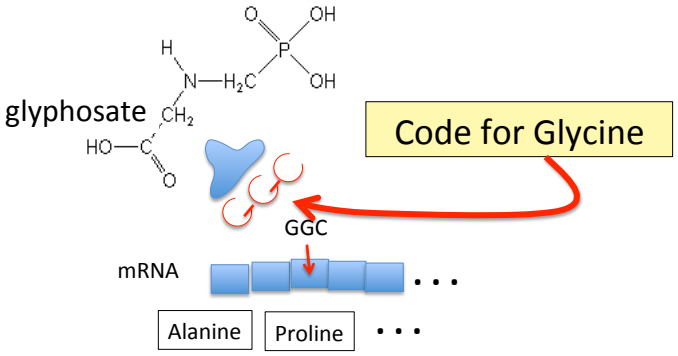

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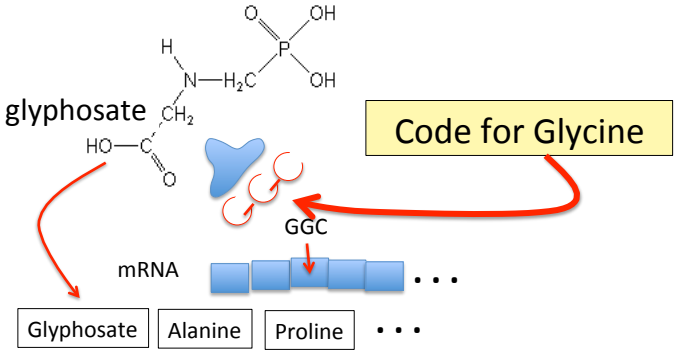
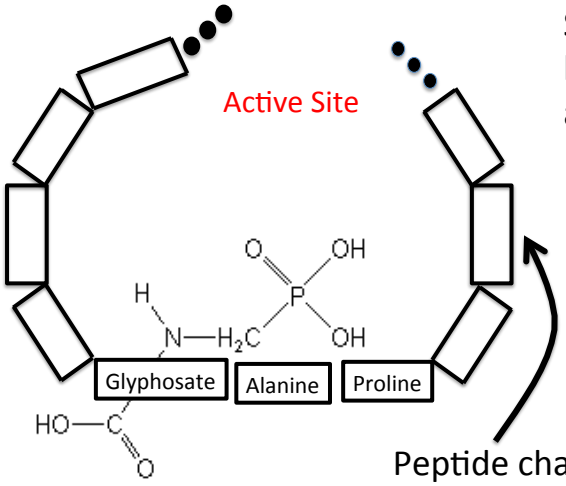
What If Glyphosate Could Insert Itself Into Protein Synthesis???



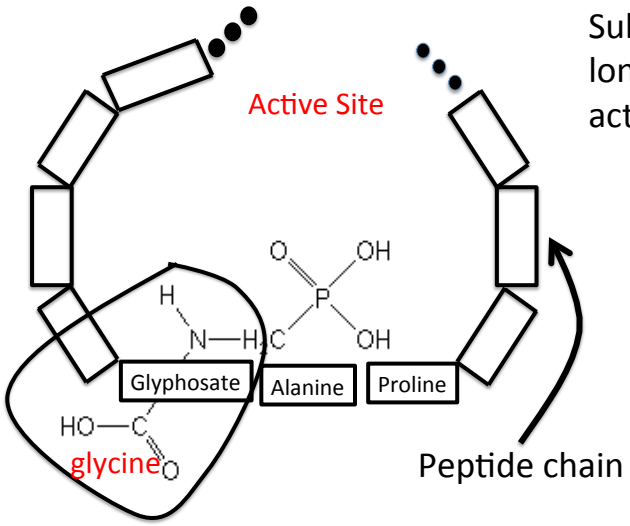
-- Any proteins with conserved glycine residues are likely to be affected in a major way

Extra Piece Sticks Out at Active Site



Substrate no longer fits in active site

Extra Piece Sticks Out at Active Site



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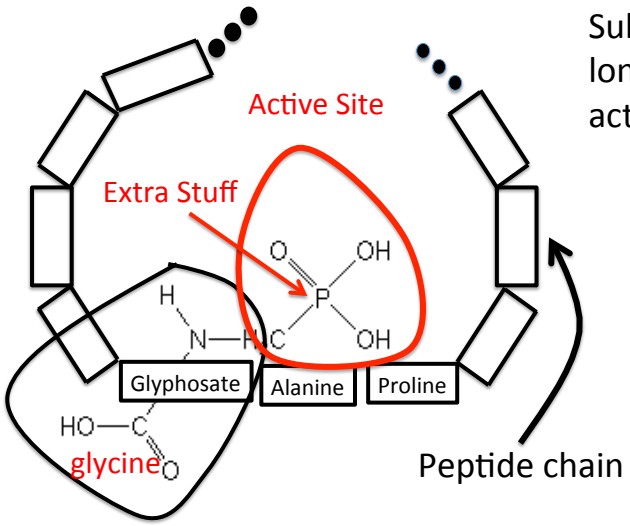

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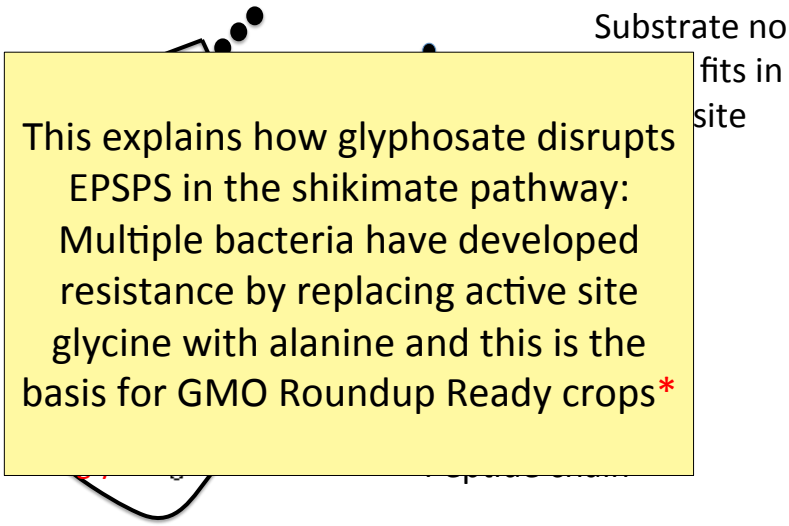


This explains how glyphosate disrupts EPSPS in the shikimate pathway: Multiple bacteria have developed resistance by replacing active site glycine with alanine and this is the basis for GMO Roundup Ready crops*

*T Funke et al., Molecular basis for the herbicide resistance of Roundup Ready crops. PNAS 2006;103(35):13010-13015.

Inhibition of EPSPS by glyphosate: Resistant E coli mutant*

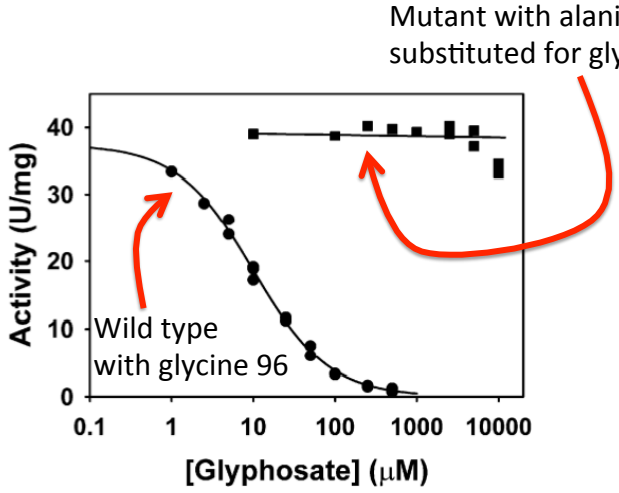


*Figure 3, S Eschenburg et al. Planta 2002;216:129-135.

Some Predicted Consequences*

- Neural tube defects
- Autism
- Impaired collagen → osteoarthritis
- Steatohepatitis (fatty liver disease)
- Obesity and adrenal insufficiency
- Hypothyroidism
- Impaired iron homeostasis and kidney failure
- Insulin resistance and diabetes
- Cancer

*A. Samsel and S. Seneff. Journal of Biological Physics and Chemistry 2016;16:9-46.

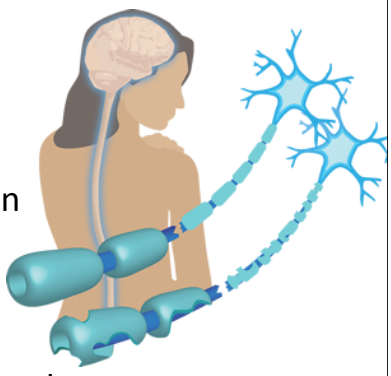
An Analogy: ALS in Guam

- An epidemic in ALS in Guam was traced to a natural toxin found in cycads
- BMAA is a non-coding amino acid that gets inserted by mistake in place of serine

- Defective versions of a glutamate transporter have been linked to ALS*
- The transporter has an essential serine-rich region in its sequence**

*Antioxidants & Redox Signaling 2009;11: 1587-1602.
**DJ Slotboom et al., PNAS 1999; 96(25): 14282-14287.

Another Analogy: MS & Sugar Beets*



- Sugar beets contain an analogue of proline called Aze
- Remarkable correlation between MS frequency and proximity to sugar beet agriculture
- Myelin basic protein contains a concentration of proline residues that are absolutely essential for its proper function

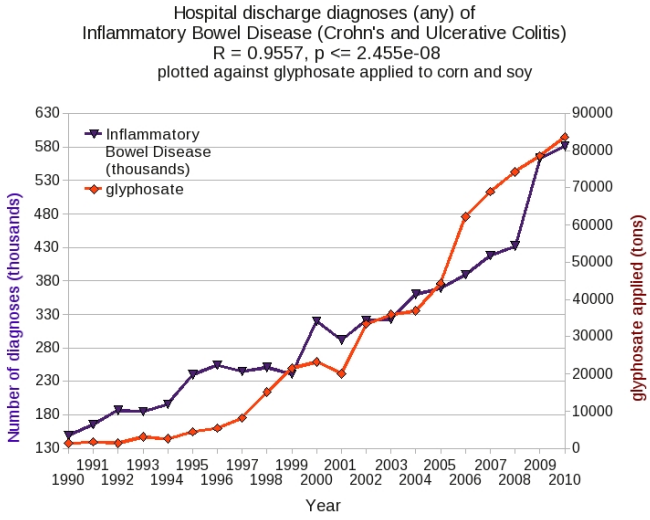
*E. Rubenstein, J Neuropathol Exp Neurol 2008;67(11): 1035-1040.

How Glyphosate Disrupts Methylation and Sulfation

Human Digestive System Disorders

- Alarming increase in the US in many diseases related to the gut
  - Crohn's disease, inflammatory bowel disease, colitis, acid reflux disease, gluten and casein intolerance, celiac disease, leaky gut
- The gut-brain axis links neurological disorders with gut disorders
- I believe that glyphosate is a major cause

Inflammatory Bowel Disease and Glyphosate Usage*

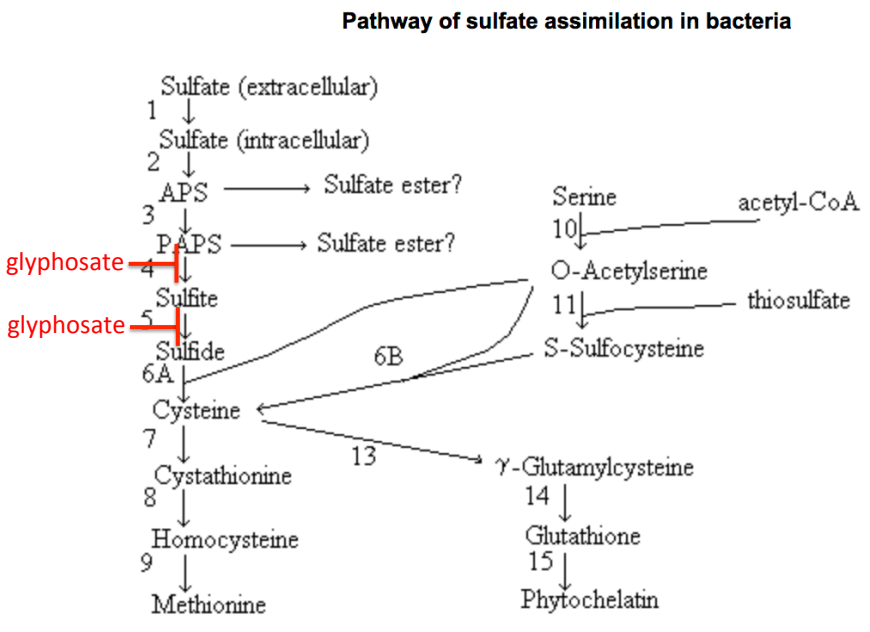


*Plot provided by Dr. Nancy Swanson

IBD Under 5 Years Old in Canada: An Epidemic*

- Canada has among the highest rates of childhood-onset IBD in the world
- Incidence is rapidly rising in children under 5 (7.2% increase per year since 1999)
  - Suspect early-life environmental triggers
- Canadian government's extensive database of glyphosate residues in foods shows by far highest levels in foods from Canada or the US

*El Benchimol et al., Am J Gastroenterol 2017;112(7):1120-1134.



Proteins Suppressed by Glyphosate in *E. coli**

PAPS reductase	-3.75
sulfite reductase, alpha subunit	-3.23
sulfite reductase, beta subunit	-4.55
periplasmic sulfate-binding protein	-3.39
sulfate transport system permease	-2.05

*W. Lu et al., Mol BioSyst 2013; 9: 522-530, Supplementary Table S2.

Proteins Suppressed by Glyphosate in *E. coli**

Required for incorporation of inorganic sulfur from sulfate into organic sulfur (methionine)

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sulfite reductase, be	
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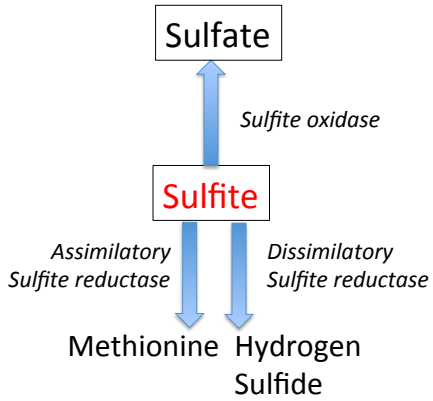
Required for transport of sulfate into the cell

*W. Lu et al., Mol BioSyst 2013; 9: 522-530, Supplementary Table S2.

Sulfite Metabolism: Sulfur Sensitivity



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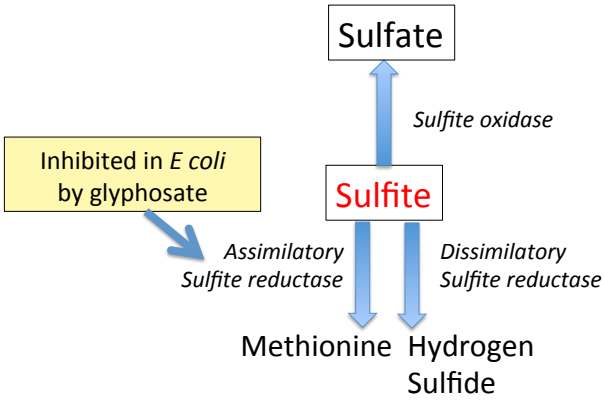

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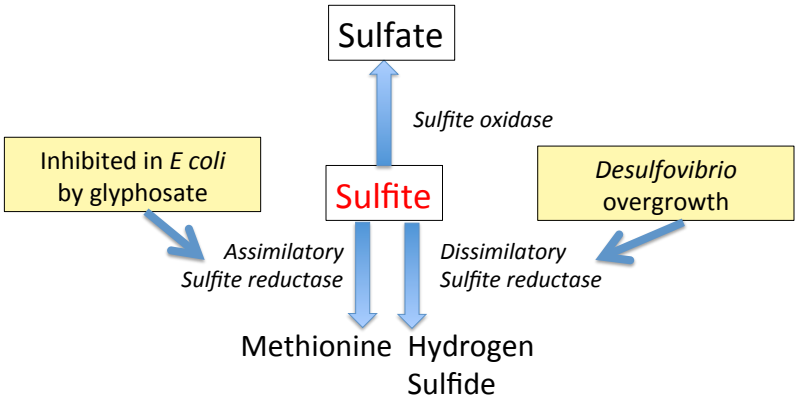

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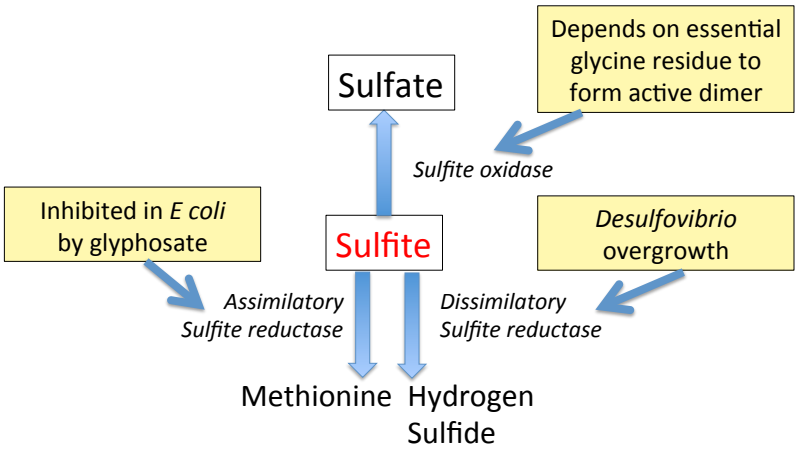
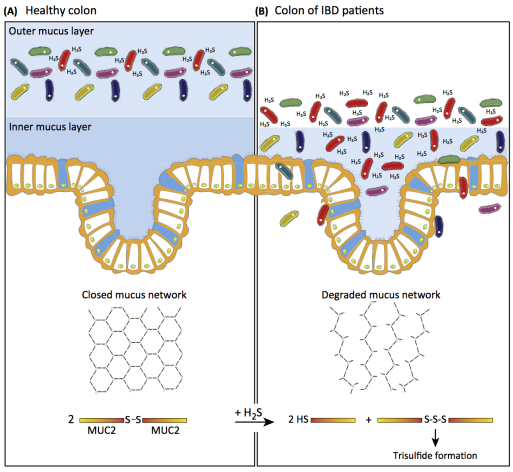


"Sulfide as a Mucus Barrier-Breaker in Inflammatory Bowel Disease?"*

"hydrogen sulfide concentrations rise, causing denaturation of the outer and inner mucus layers, thereby allowing penetration and contact of bacteria with the host epithelial lining. This in turn triggers inflammation."



*N. Ijssennagger et al., Trends in Molecular Medicine 2016;22(3): 190-199.

Conserved Glycines in Important Sulfur-processing Enzymes

- The sulfotransferases*
  - GxxGxxK motif required for binding PAPS
- Sulfite oxidase**
  - Changing glycine at residue 473 with aspartate destroys enzyme activity
  - Aspartate has similar properties as glyphosate, being bulky and negatively charged
  - Defective SO leads to severe birth defects and neurological problems that usually result in death at an early age

*K. Komatsu et al., Biochemical and Biophysical Research Communications 1994;204(3): 1178-1185.
**H.L. Wilson et al., Biochemistry 2006, 45, 2149-2160.

Sulfate Reducing Microbes

- Desulfovibrio is a microbe in the colon that reduces sulfate to hydrogen sulfide gas
  - Desulfovibrio overgrowth is linked to autism
- Hydrogen sulfide travels like a ghost across all tissues
  - It can travel by diffusion from the colon to the spinal column, the pancreas, the liver, etc.
  - It can be oxidized to form sulfate at the destination site, but this requires superoxide, leading to local tissue damage

Sulfate Reducing Microbes

- Desulfovibrio is a microbe in the colon that
- This is a novel way to transport sulfate!
  - It can travel by diffusion from the colon to the spinal column, the pancreas, the liver, etc.
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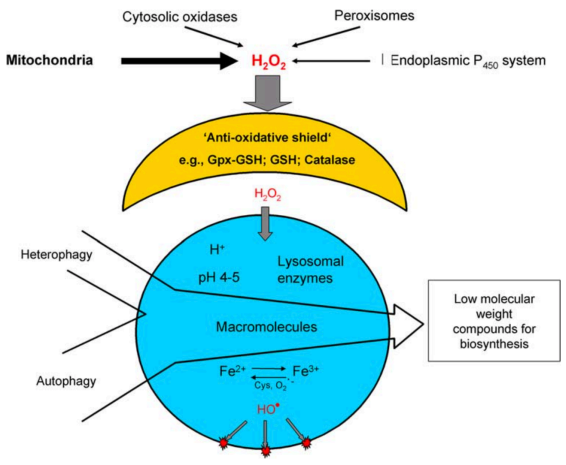
How Glyphosate Damages Mitochondria and Lysosomes



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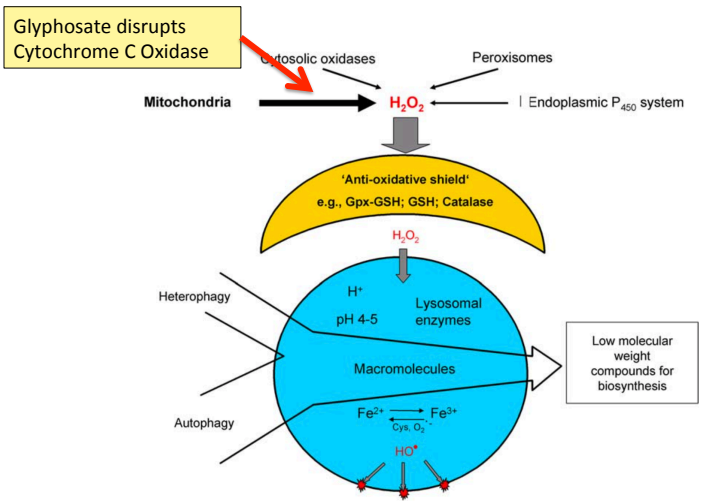

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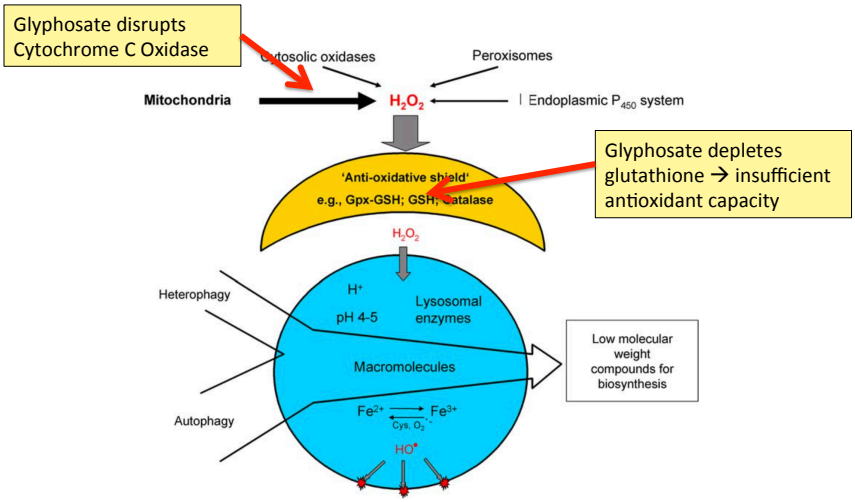

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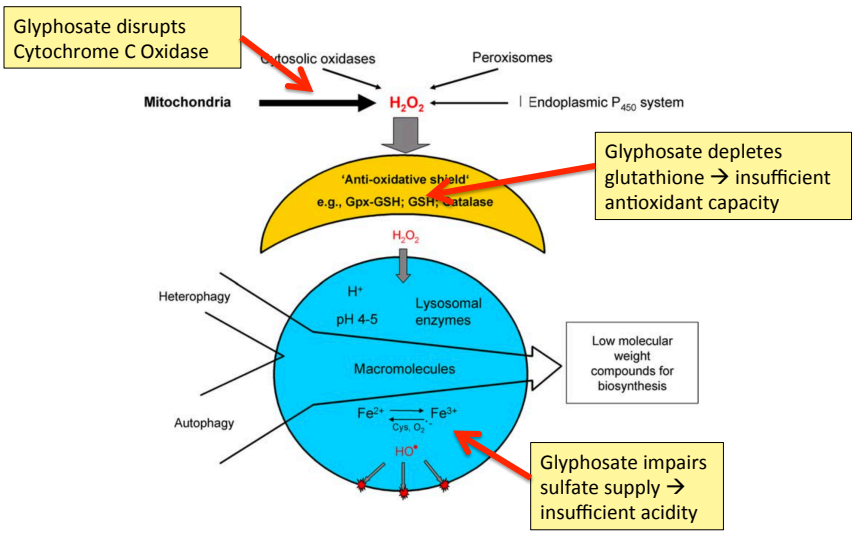

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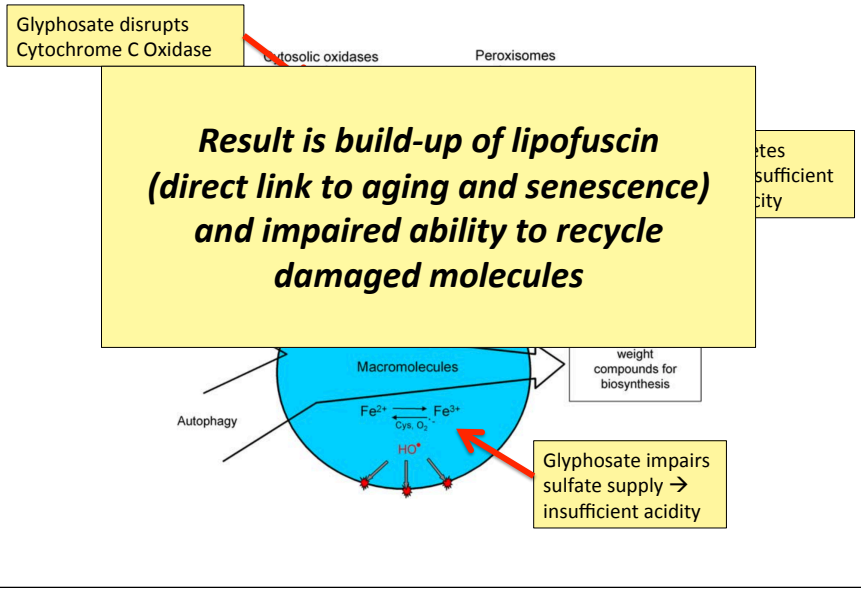

Glycine decarboxylase deficiency causes neural tube defects and features of non-ketotic hyperglycinemia in mice*

- Fascinating article about mice with a deficiency in a protein involved in generating methyl groups from glycine -> methylfolate deficiency
- These mice have very high rate of neural tube defects
- Those that are viable have swollen ventricles (a feature of autism) and delayed development
- Methylation pathway impairment is a common feature of autism

*YJ Pai et al., Nature Communications 2015; 6:6388

Glycine decarboxylase deficiency causes neural tube defects and features of non-ketotic hyperglycinemia in mice*

- Fascinating article about mice with a deficiency in

Glycine decarboxylase has a glycine-rich region that maintains shape and flexibility of active site**

- Those that are viable have swollen ventricles (a feature of autism) and delayed development
- Methylation pathway impairment is a common feature of autism

**A Kume et al., JBC 1991; 266(5): 3323-3329

Inflammation and Hydrogen Sulfide*

- Enhanced H_2S synthesis in multiple inflammatory diseases and conditions
  - arthritis
  - acute pancreatitis
  - sepsis
  - hemorrhagic shock
  - burns

- H_2S is synthesized from cysteine and then oxidized to form sulfate
- H_2S induces inflammatory response which supplies superoxide needed for sulfate formation

*N Muniraj et al., Int J Rheum Dis. 2017 Feb;20(2):182-189.

Inflammation and Hydrogen Sulfide*

- Enhanced H_2S synthesis in multiple inflammatory diseases and conditions

Is this a mechanism to renew sulfate supplies to the vasculature?

- H
oxidized to form sulfate
- H_2S induces inflammatory response which supplies superoxide needed for sulfate formation

*N Muniraj et al., Int J Rheum Dis. 2017 Feb;20(2):182-189.

Microcephaly and Prematurity*

- Data pooled from hospitals in 11 cities in 5 states
- 1506 premature infants were studied (GA 23-28 weeks)
- Microcephaly occurs much more commonly than expected among babies born prematurely
  - 2.2% expected, nearly 10% observed
- Extremely low gestational age and severe intra-uterine growth restriction are risk factors for microcephaly
  - Intra-uterine growth restriction caused by inflamed and damaged placenta

*TF McElrath et al., Am J Obstet Gynecol. 2010; 203(2): 138.e1–138.e8.

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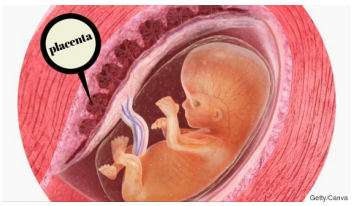
Hypothesis: Inflamed placenta is trying to recover adequate sulfate by oxidizing reduced sulfur sources

*TF McElrath et al., Am J Obstet Gynecol. 2010; 203(2): 138.e1–138.e8.

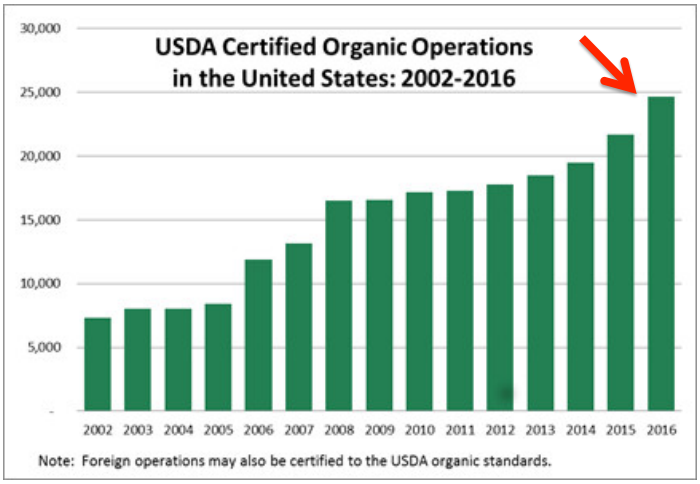
Magnesium Sulfate Protects Placenta from Inflammation*



- Rat model: inject LPS to induce inflammation in placenta
- Placentas responded with increased expression of inflammatory markers
- Simultaneous administration of magnesium sulfate protected placentas
- Human placental cultures reacted similarly to both LPS and magnesium sulfate

*O Dowling et al. Placenta 2012;33(5):392-8.

This is Good News!*



*https://www.ams.usda.gov/press-release/2016-count-certified-organic-operations-shows-continued-growth-us-market

Summary

- Glyphosate usage has grown exponentially over the past two decades, in step with the introduction of GMO Roundup-Ready crops
- Glyphosate causes neural tube defects and autism through multiple metabolic disruptions
  - Folate and methionine deficiency
  - Disrupted sulfate synthesis and transport
- Methionine sits at the crossroads of the methylation and transsulfuration pathways
- Folate deficiency due to glyphosate's disruption of gut microbes led to regulation to require folic acid fortification of wheat-based foods
- Folic acid is a defective form of folate that causes liver disease and increased risk to autism and asthma
- Cholesterol sulfate, heparan sulfate and chondroitin sulfate are essential for fetal brain development