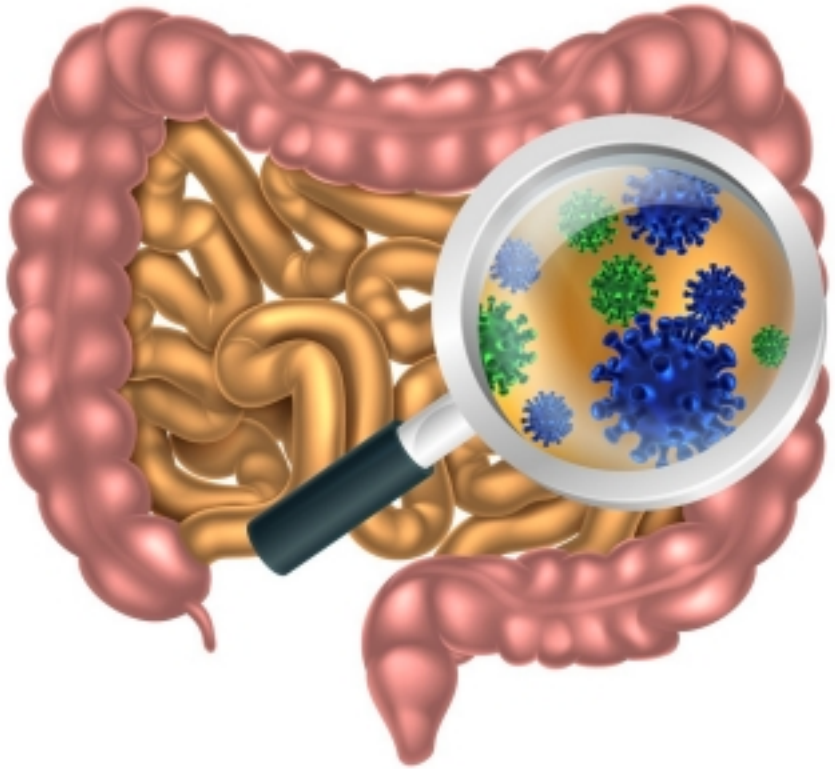


Glyphosate and the Gut

Stephanie Seneff
MIT CSAIL
AutismOne 2018

Outline

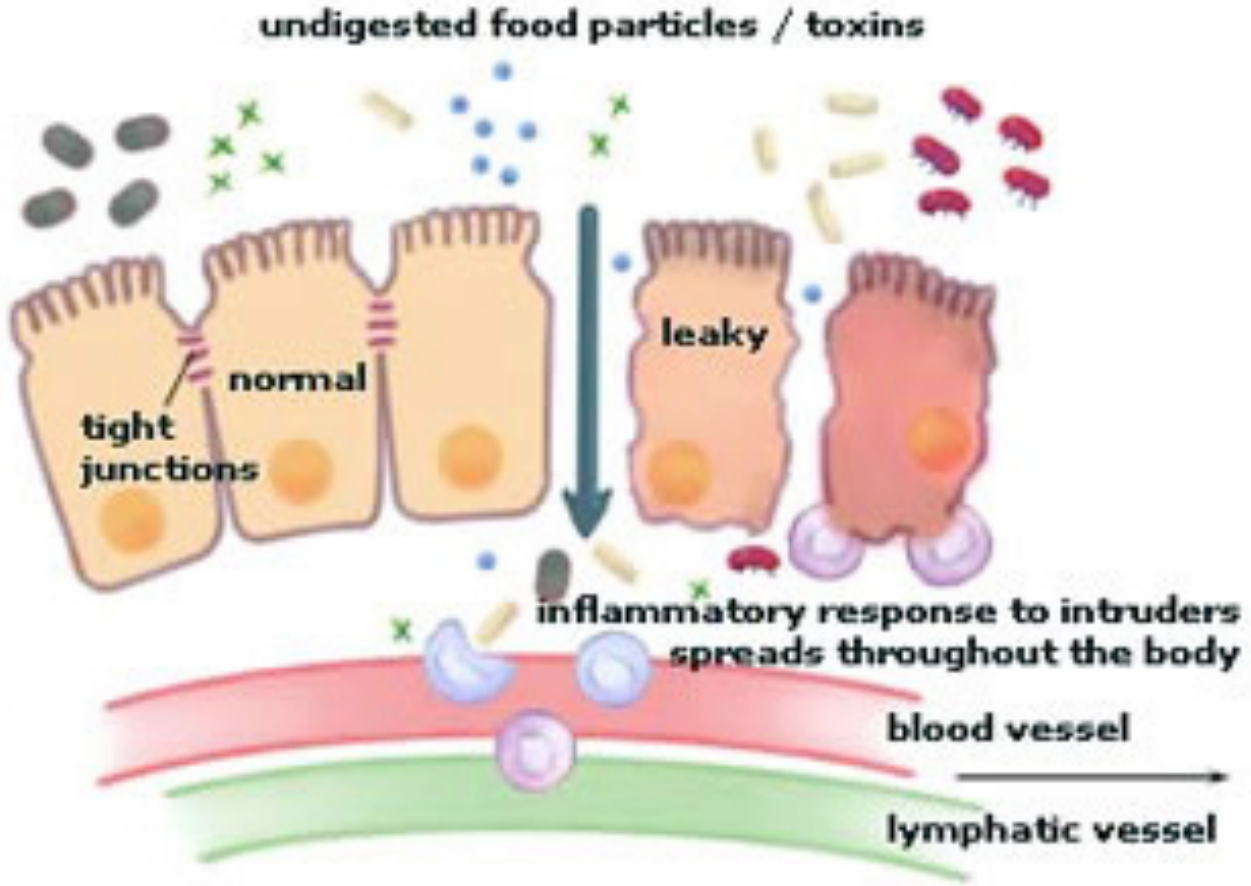
- Autism and Gut Issues
- Pathogen Overgrowth
- Digestive Enzyme Impairment
- Celiac disease
- Antibiotic Resistance
- BTBR Mouse model of Autism
- Impaired CYP enzymes and Bile Acid Synthesis
- Impaired Myosin and Peristalsis
- Clostridia Overgrowth and Autism
- Summary

Autism and the Gut*

"Prospective, controlled studies suggest that as many as 70% of autistic children exhibit chronic GI-related symptoms [1,5,6] including diarrhea, laxative-dependent constipation, abdominal distension, failure to thrive, weight loss, feeding problems, and abdominal pain related to extreme irritability, aggression, and self-injury."

*SJ Walker et al. PLOS One March 2013; 8(3):e58058.

LEAKY GUT


undigested food particles / toxins
normal
tight
junctions
leaky
inflammatory response to intruders
spreads throughout the body
blood vessel
lymphatic vessel

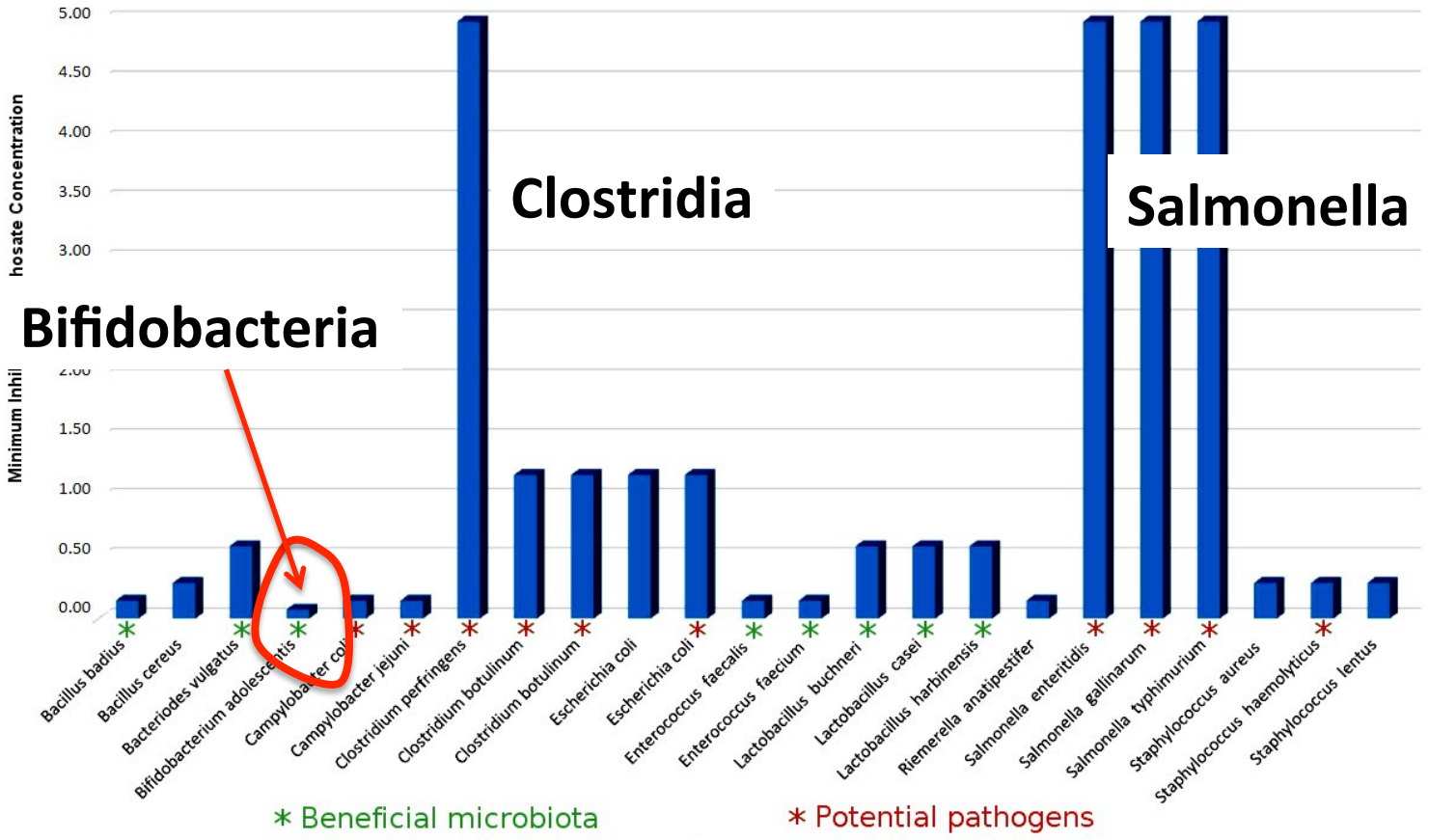
Glyphosate and the Gut: Pathogen Overgrowth

- Glyphosate is an antimicrobial agent that preferentially kills beneficial microbes, allowing pathogens to flourish in the gut*
- Immune cells invade the gut and release inflammatory cytokines
  - This causes increased risk to inflammatory bowel diseases such as Crohn's and ulcerative colitis

* Samsel and Seneff. Entropy 2013; 15: 1416-1463.

Pathogen Overgrowth in Poultry Microbes Exposed to Glyphosate*

Shehata AA, Schrödl W, Aldin AA, Hafez HM, Krüger M. The effect of glyphosate on potential pathogens and beneficial members of poultry microbiota in vitro. Curr Microbiol. 2013 Apr;66(4):350-8.



*Plot provided by Dr. Martin Michener

Glyphosate and the Gut: Digestive Enzymes

- Glyphosate has been found as a contaminant in digestive enzymes trypsin, pepsin and lipase*
- Trypsin impairment prevents proteins like gluten in wheat from being digested
- Undigested proteins induce release of zonulin which opens up gut barrier**
- Zonulin lingers because trypsin is defective

*A Samsel and S Seneff. J Biol Phys Chem 2017;17:8-32

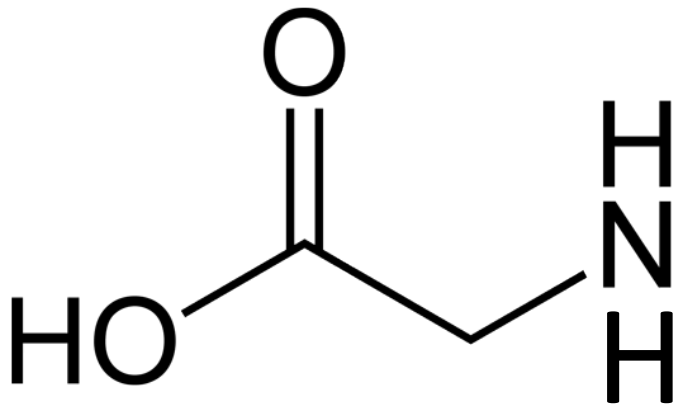
** JJ Gildea et al. J Clin Nutr Diet. 2017, 3:1.

Trypsin, Pepsin and Lipase are all contaminated with glyphosate*

Enzyme	Glyphosate (PPB)
Pepsin (ELISA)	<40
Pepsin (GC-MS)	430
Pepsin (HPLC-MSMS)	290
Trypsin (ELISA)	62
Lipase (ELISA)	24

*A Samsel and S Seneff. Journal of Biological Physics and Chemistry 2017;17: 8-32

Glyphosate is a non-coding amino acid analogue of glycine



Glycine

Glyphosate

Glyphosate is a non-coding amino acid analogue of glycine

Glyphosate substitution by mistake for glycine during protein synthesis could explain glyphosate contamination in trypsin

Glyphosate

Trypsin, Pepsin and Lipase are all contaminated with glyphosate*

Trypsin's activation domain contains four crucial glycine rich subdomains:*

N-terminus to Gly 19

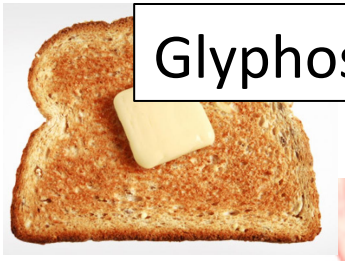
Gly 142 to Pro 152

Gly 184 to Gly 193

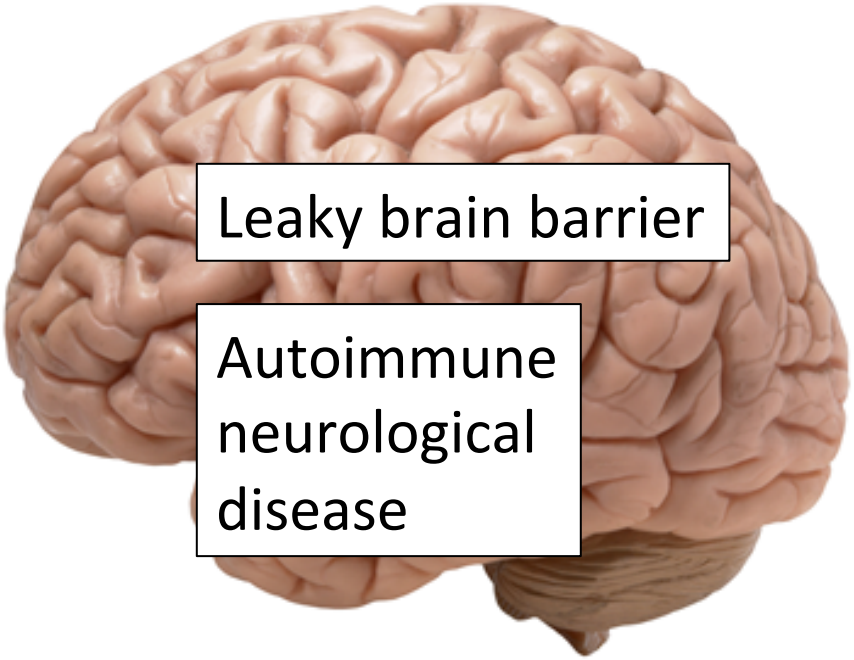
Gly 216 to Asn 223

*A Samsel and S Seneff. Journal of Biological Physics and Chemistry 2017;17: 8-32

A Scenario for Gluten Intolerance



Glyphosate in wheat

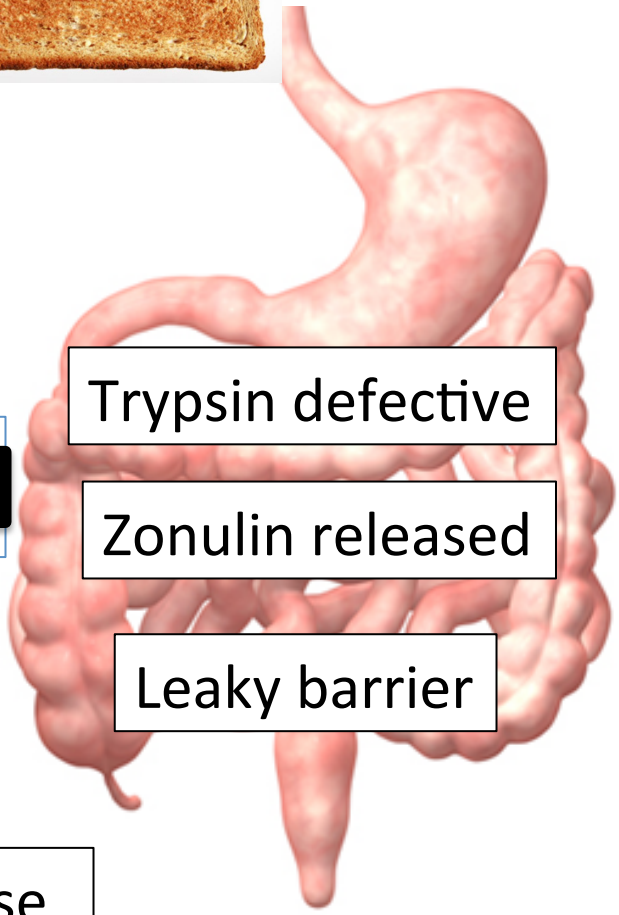


Leaky brain barrier

Autoimmune neurological disease

Zonulin

Gliadin



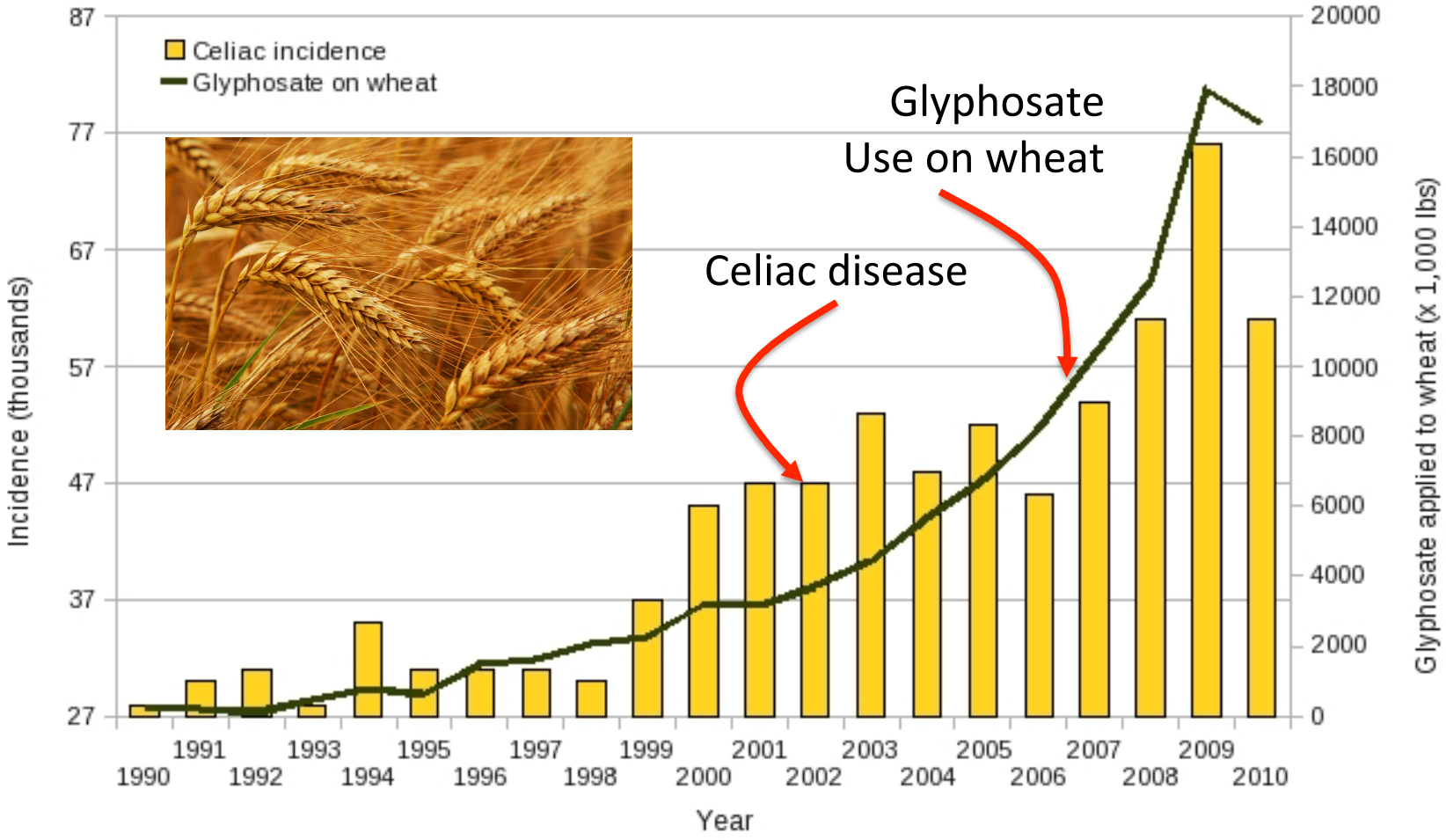
Trypsin defective

Zonulin released

Leaky barrier

Systemic immune response induces multiple complex symptoms

Glyphosate and Celiac Disease*



*Samsel and Seneff, Interdiscip Toxicol. 2013;**6**(4): 159–184.

Celiac Disease, Glyphosate and Non Hodgkin's Lymphoma

- Glyphosate preferentially kills *Bifidobacteria**
- Bifidobacteria are depleted in celiac disease**
- Celiac disease is associated with increased risk to non Hodgkin's lymphoma***
- Glyphosate itself is also linked directly to non Hodgkin's lymphoma****

*A.A. Shehata et al., Curr Microbiol. 2013 Apr;66(4):350-8.

** M. Velasquez-Manoff, NY Times Sunday Review, Feb. 23, 2013.

*** C. Catassi et all, JAMA. 2002 Mar 20;287(11):1413-9.

****M. Eriksson et al., Int J Cancer. 2008 Oct 1;123(7):1657-63.

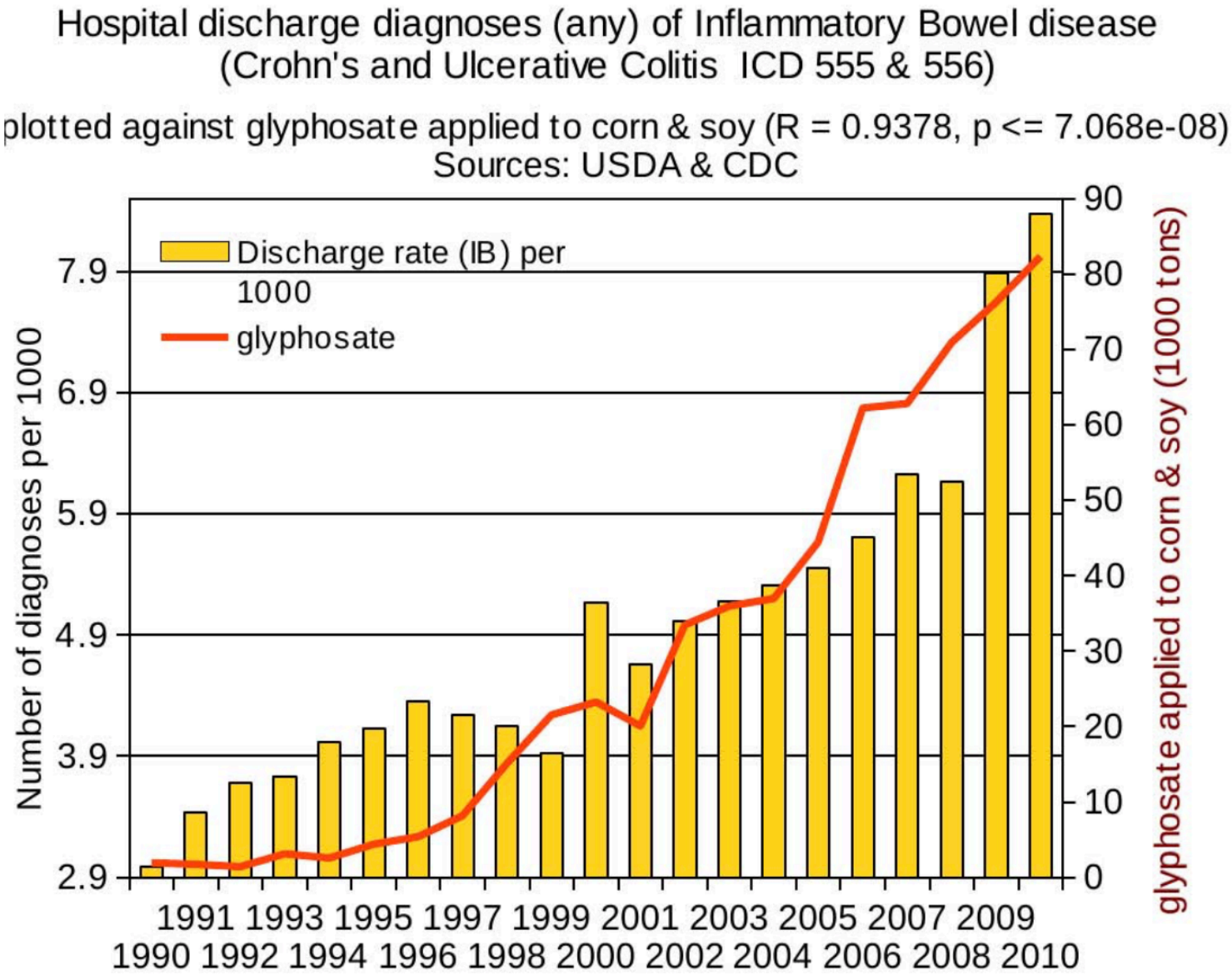
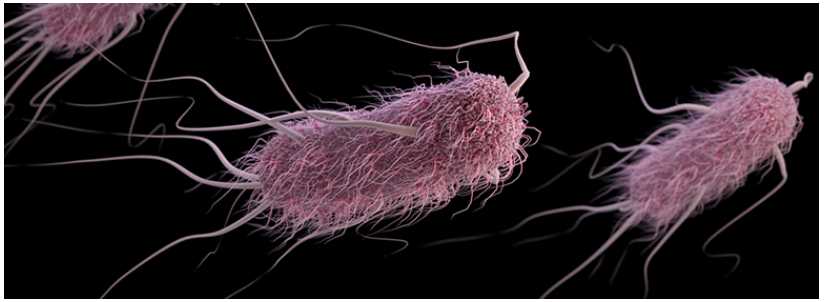


*Figure 20, NL Swanson et al. Journal of Organic Systems 9(2), 2014, p. 25.

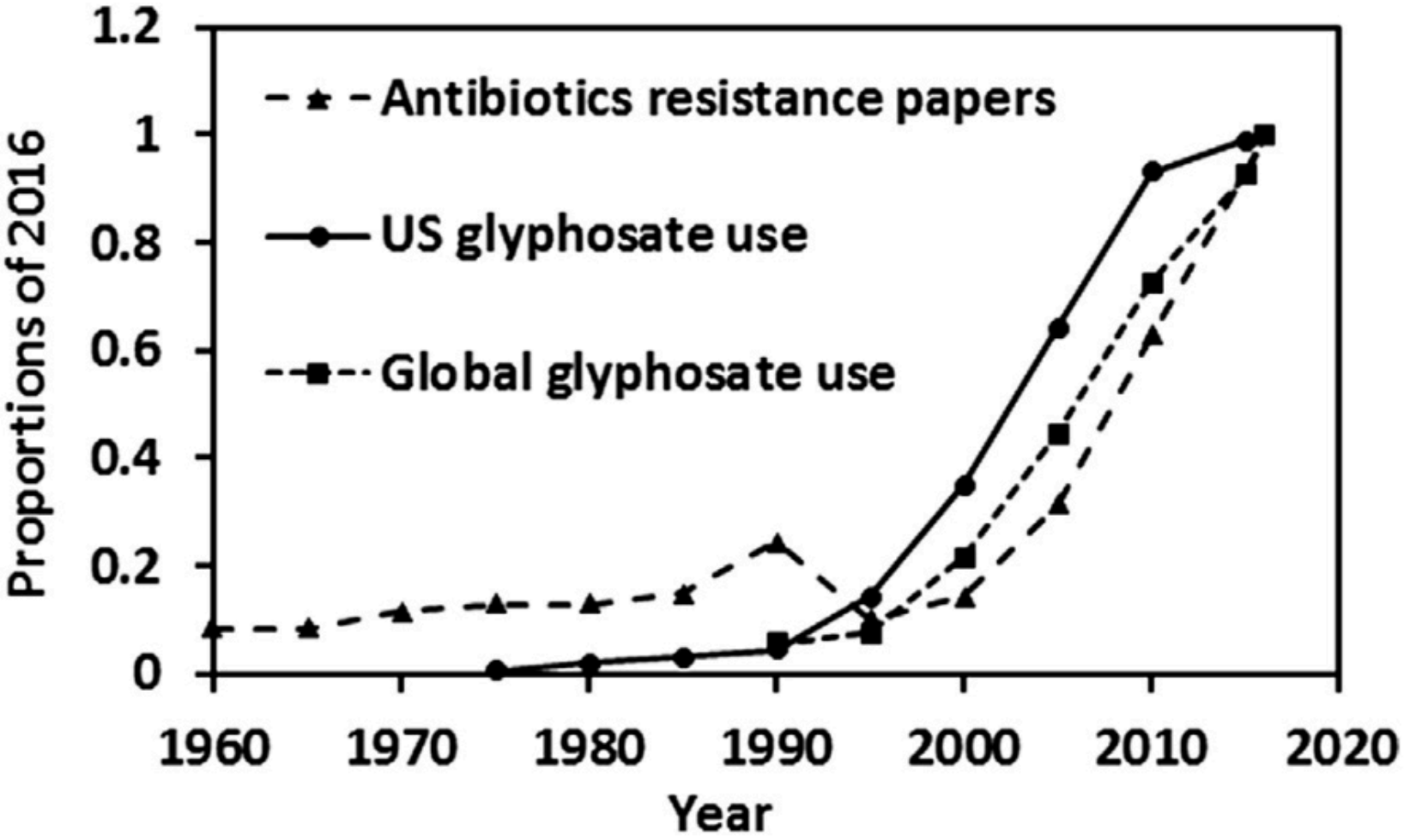
Glyphosate Induces Antibiotic Resistance*



- Actinobacteria produce a free radical scavenger in response to glyphosate that provides resistance to a wide range of antibiotics, including penicillin
- E. coli exposed to glyphosate develop an "efflux pump" that increases resistance to the fluoroquinolone Ciprofloxacin and the aminoglycoside Kanamycin.
  - Same effect observed in Salmonella exposed to glyphosate

*AHC Van Bruggen et al. Science of the Total Environment 2018;616-617: 255–268.

Glyphosate Usage and Papers on Antibiotic Resistance*



*AHC Van Bruggen et al. Science of the Total Environment 2018;616-617: 255–268.

A BTBR Mouse Model of Autism*

These mice had all the mouse features of autism
They were fed "standard rodent chow" – glyphosate contaminated?

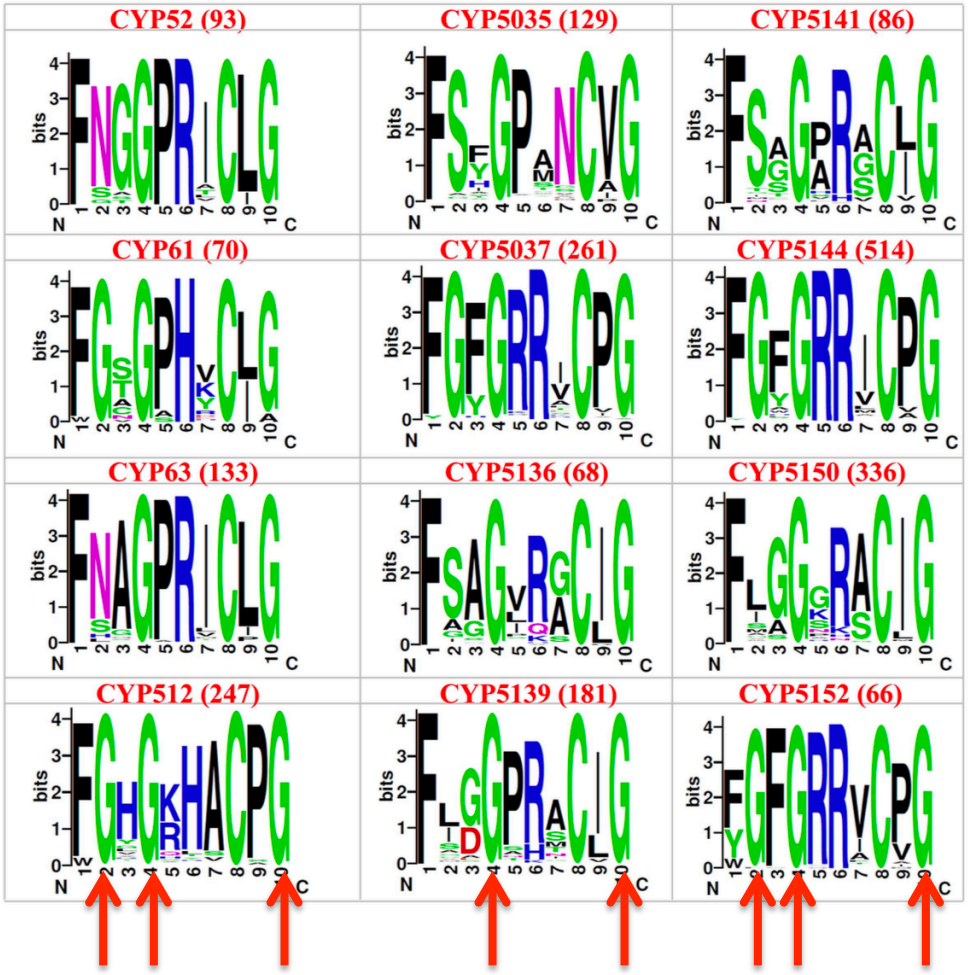
Some features in the gut:

- Reduced levels of bile acids (due to impaired CYP7A1 activity in the liver)
- Further reduced levels of secondary bile acids (impaired metabolism by gut microbes)
- Reduced levels of Lactobacillus and Bifidobacteria (microbes that metabolize bile acids)
  - These microbes are preferentially killed by glyphosate
- Serotonin deficiency (due in part to tryptophan conversion to kynurenine to fight infection)
  - Serotonin is derived from tryptophan, a product of the shikimate pathway which glyphosate disrupts

*AV Glubeva et al. EBioMedicine. 2017 Oct;24:166-178.

Glyphosate Disrupts Cytochrome P450 (CYP) Enzymes*

- Glyphosate has been shown to severely suppress CYP enzymes in rat liver
- CYP enzymes have a unique FXXGXRXCXG motif with two and sometimes three critical glycine residues**



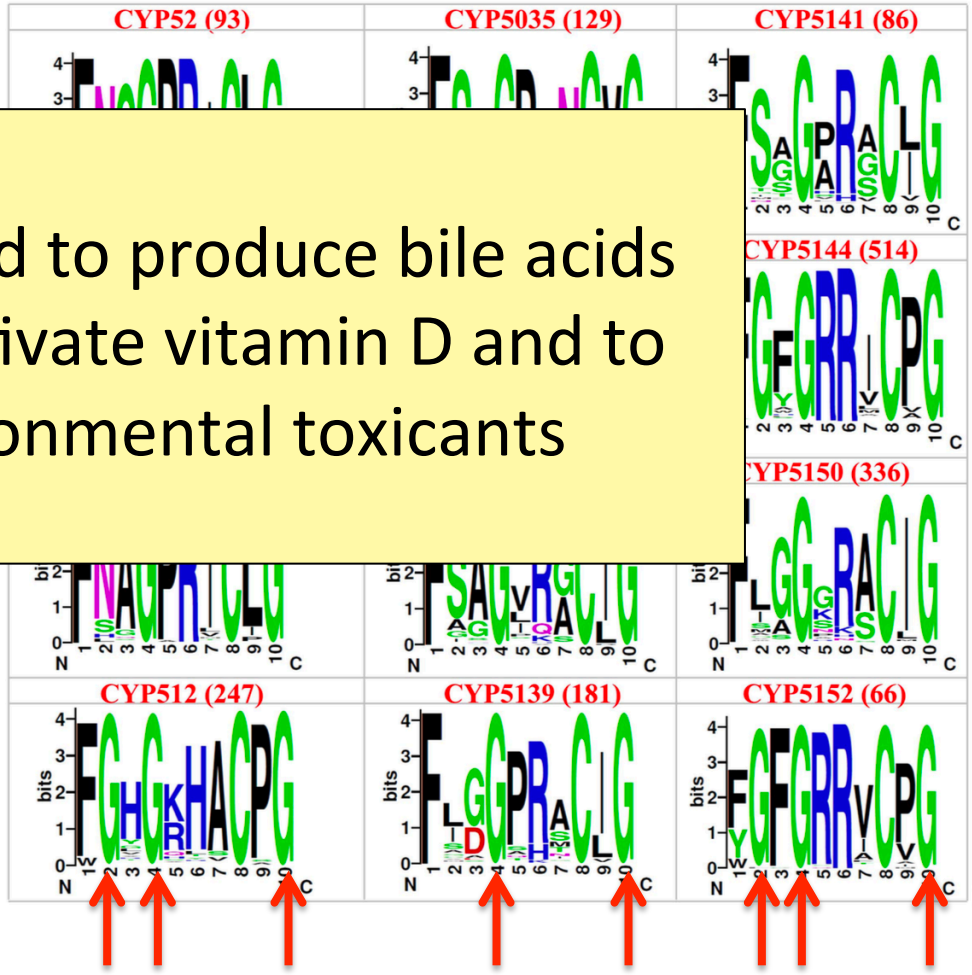
*A Samsel and S Seneff. Entropy 2013; 15: 1416-1463.

**K Syed and SS Mashele. PLOS ONE 2014; 9(4):| e95616.

Glyphosate Disrupts Cytochrome P450 (CYP) Enzymes*

- Glyphosate has been
- unique FXXGXRXCXG motif with two and sometimes three critical glycine residues**

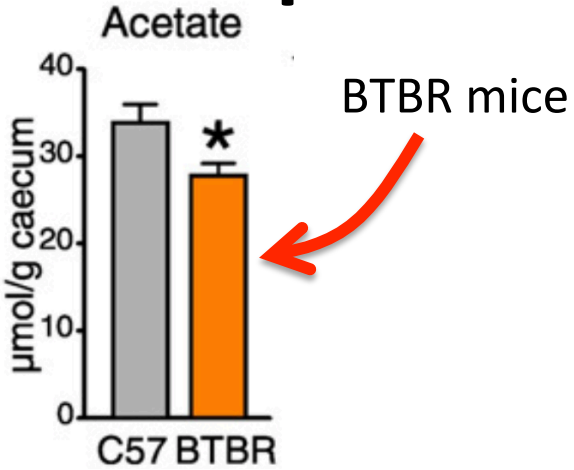
CYP enzymes are needed to produce bile acids for digesting fats, to activate vitamin D and to detoxify many environmental toxicants



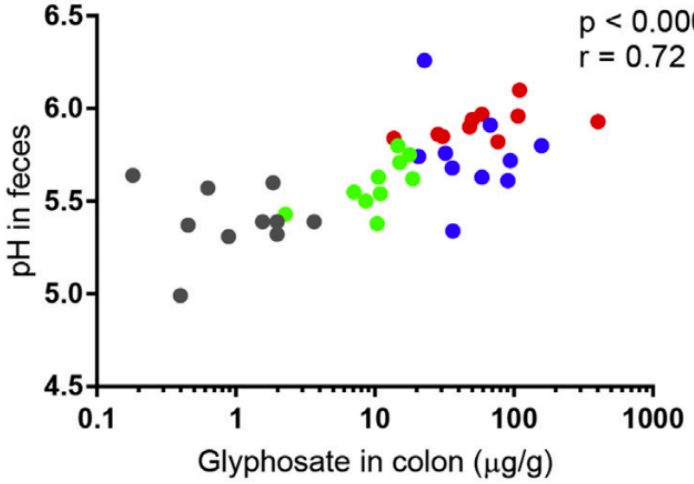
*A Samsel and S Seneff. Entropy 2013; 15: 1416-1463.

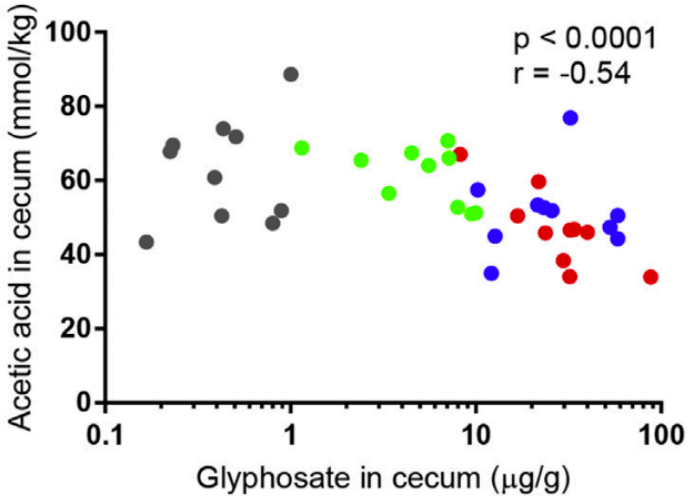
**K Syed and SS Mashele. PLOS ONE 2014; 9(4):| e95616.

BTBR mice have low acetate, and glyphosate disrupts acetate synthesis in gut*



Children with autism had only 3.5 mg/ml acetate in stool samples compared to 5.1 in controls.**

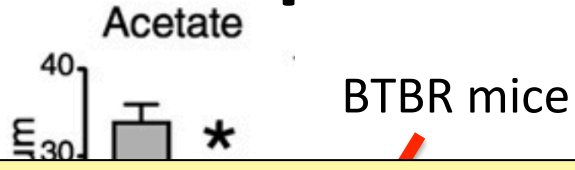




*LN Nielsen et al. Environmental Pollution 2018;233:364e376.

**Adams et al. BMC Gastroenterology 2011; 11:22.

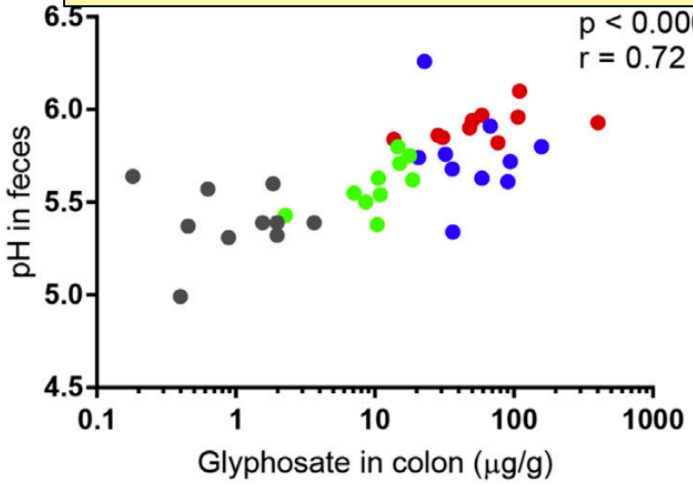
BTBR mice have low acetate, and glyphosate disrupts acetate synthesis in gut*

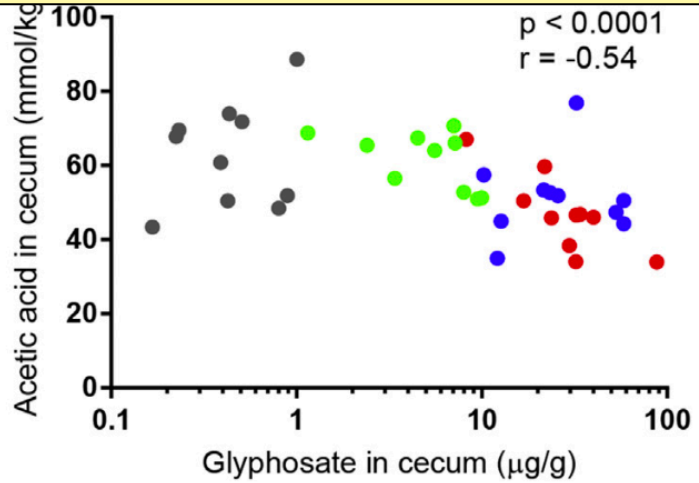


BTBR mice

Children with autism had

Elevated pH linked to glyphosate exposure results in small intestinal bacterial overgrowth (SIBO)





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Glyphosate, Pathogens, Autism*

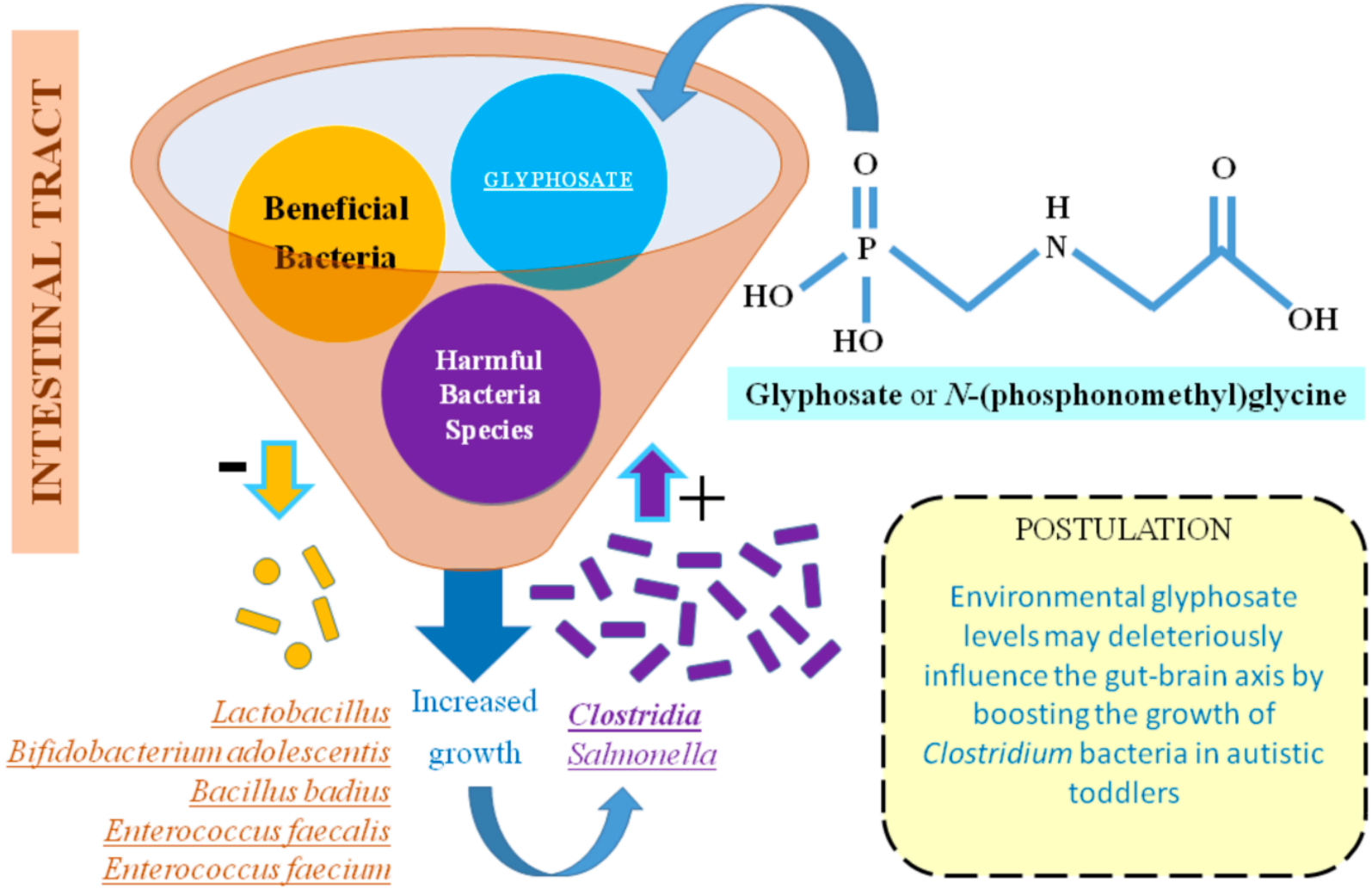
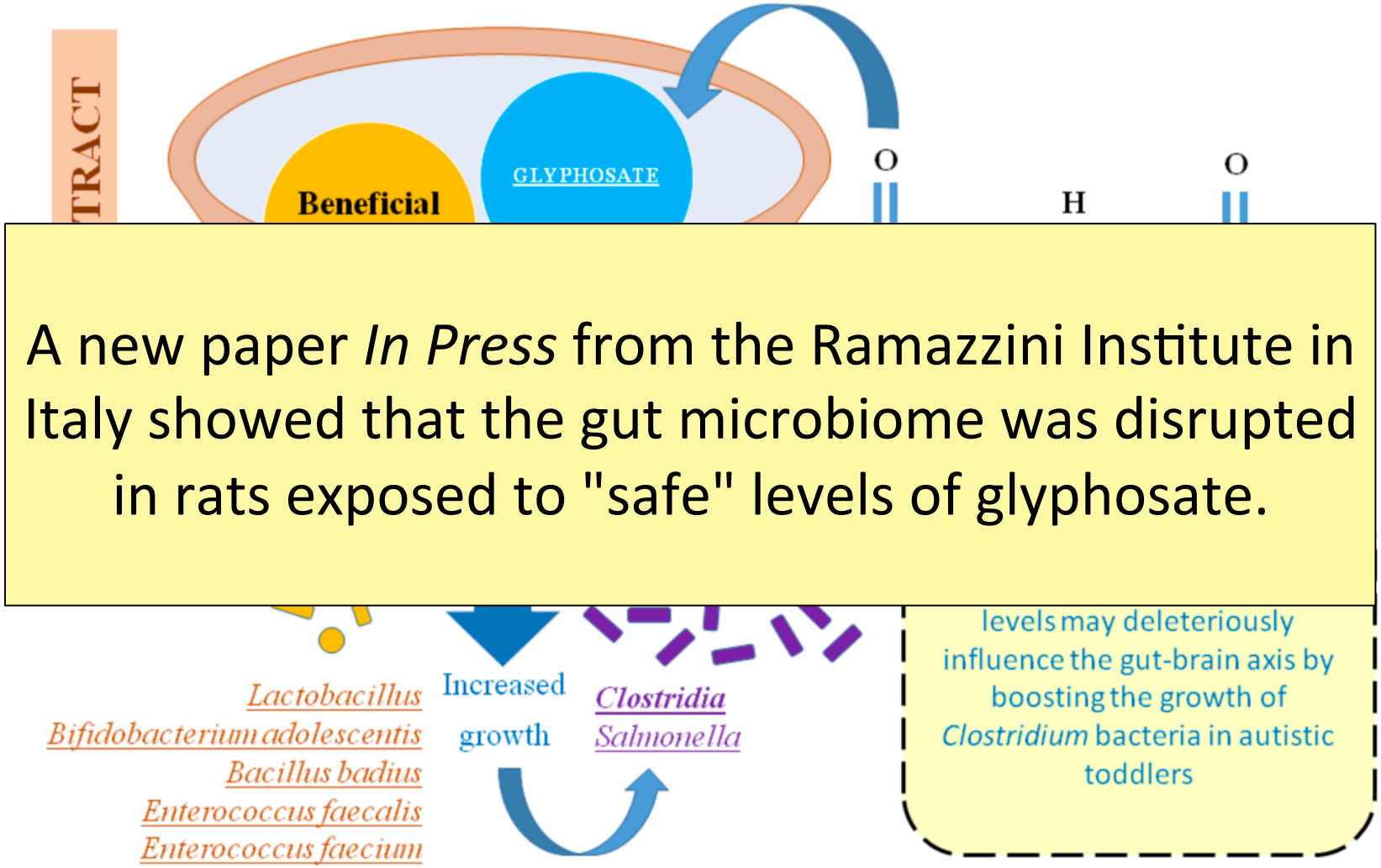


*Figure 2. I Argou-Cardozo and F Zeidán-Chuliá. Med. Sci. 2018; 6: 29.

Glyphosate, Pathogens, Autism*



A new paper *In Press* from the Ramazzini Institute in Italy showed that the gut microbiome was disrupted in rats exposed to "safe" levels of glyphosate.

*Figure 2. I Argou-Cardozo and F Zeidán-Chuliá. Med. Sci. 2018; 6: 29.

Evidence Linking Autism to Clostridia Overgrowth*

- 14 autistic children with gut disorder compared to 21 controls
- Significant increase in *Clostridia* species in the gut in autistic children
- Associated with reduced tryptophan levels and increased expression of inflammatory markers
  - Tryptophan is a product of the shikimate pathway, which glyphosate blocks
  - Macrophages in inflamed tissue take up tryptophan, reducing bioavailability to the brain
- Proposed role for antibiotics
  - Glyphosate is a patented antimicrobial agent (2010)

*RA Luna et al., Cellular and Molecular Gastroenterology and Hepatology 2017;3(2): 218-230

CASE REPORT

Elevated Urinary Glyphosate and Clostridia Metabolites With Altered Dopamine Metabolism in Triplets With Autistic Spectrum Disorder or Suspected Seizure Disorder: A Case Study *

William Shaw, PhD

- Triplets: two boys, one girl. Both boys have autism and girl has seizure disorder
- Very high levels of glyphosate in urine in all three
- *Clostridia* overgrowth due to glyphosate disruption of gut microbes
  - Clostridia produce toxins HPHPA and p-cresol, which block the conversion of dopamine to norepinephrine.
  - Damage to neurons in the brain through oxidative stress

*W. Shaw. Integrative Medicine 2017;16(1);50-57.

Myosin in the Gut

- Myosin is a motor protein found in high levels in skeletal muscles
- Myosin is also essential for gut motility (peristalsis) and for the release of bile acids into the upper intestine
- Myosin contains a highly conserved glycine at position 699*
  - If this is changed to alanine, the protein's contractile ability is reduced to less than 1%.
- Glyphosate has been shown in fish studies to suppress myosin expression**

*F Kinose et al. The Journal of Cell Biology 1996;134(4): 895-909.

**Ana Paula Rezende dos Santos et al., Chemosphere 2017;168:933e943.

Myosin in the Gut

- Myosin is a motor protein found in high levels in skeletal muscles
- SIBO (Small Intestinal Bacterial Overgrowth) is associated with impaired peristalsis*
- – If this is changed to alanine, the proteins' contractile ability is reduced to less than 1%.
- Glyphosate has been shown in fish studies to suppress myosin expression**

*AC Dukowicz et al. Gastroenterol Hepatol (N Y) 2007; 3(2): 112-122.

Summary

- Glyphosate contamination in food proteins makes them hard to break down
  - This leads to autoimmune disease
- Digestive enzymes are contaminated with glyphosate
  - Undigested proteins induce Celiac disease and leaky gut
- Glyphosate is a key factor in the emergence of antibiotic resistant pathogens
- The BTBR mouse model of autism is consistent with glyphosate damage in the gut
- Glyphosate promotes Clostridia overgrowth
  - This induces inflammatory bowel disease, an epidemic today
  - Autism has been linked to Clostridia overgrowth
  - Clostridia release toxins that induce an inflammatory response