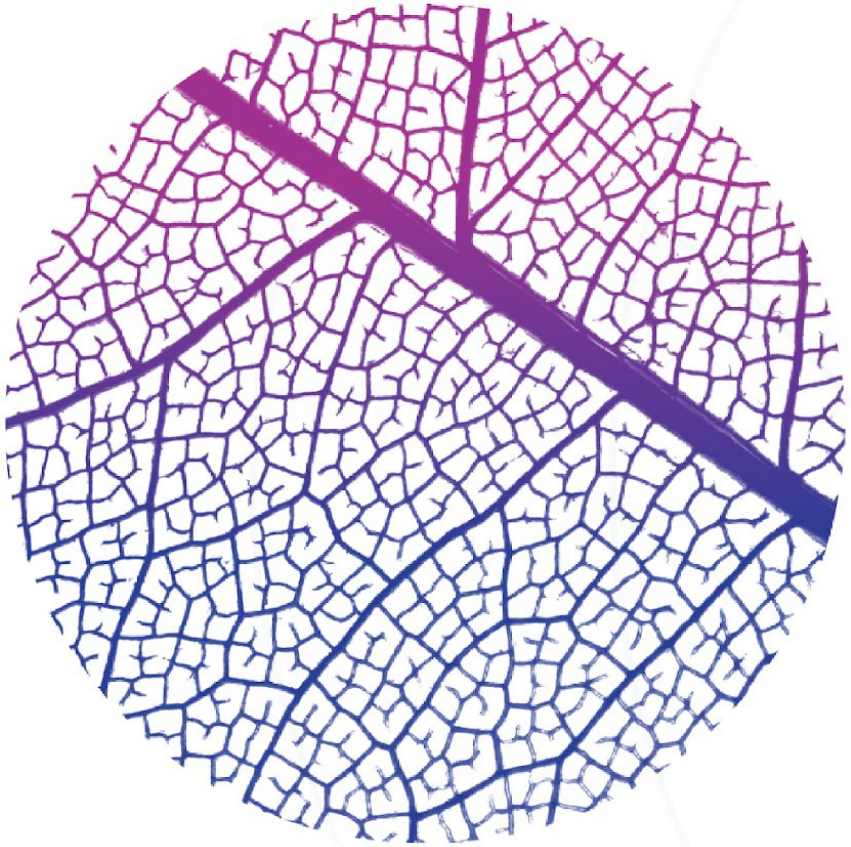


HOW TOXINS AND TOXICANTS CAN LEAD TO GUT PROBLEMS

THE ELEPHANT IN THE EXAM ROOM

LYN PATRICK, ND

Biocidin Botanicals

WHAT I'M GOING TO TALK ABOUT

Exposure to toxicants like mycotoxins, pesticides, and persistent organic pollutants can affect every system of the body, including the GI tract.

Other less known toxicants like titanium dioxide and aluminum can also lead to GI problems. Most clinicians don't look for these types of exposures because they don't know the cause and effect relationship, and they don't know how to test for them.

We'll cover common but uncommonly identified causes of gut problems through the lens of environmental medicine.

OTHER GUT TOXICANTS

- **High fructose corn syrup (HFCS)** accounts for 40% of all caloric sweeteners in the U.S. Metabolized in liver much more like ETOH than sucrose, HFCS is also metabolized in the small intestine and leads to intestinal epithelial barrier deterioration. This has been shown to increase LPS entry into bloodstream.
- **Splenda (sucralose)** is an organochlorine molecule shown in clinical studies to increase GLP-1 secretion in healthy individuals. In DMII, reduces glucagon secretion by the pancreas and delays motility. Increased glucose/insulin levels in overweight women, and alters gut microbiome in rats – *lactobacilli* and *bifidobacteria* – disproportionately affected compared to pathogenic bacteria including enterobacteria. The reduction in fecal microflora was not fully reversible even three months after cessation of sucralose.

doi.org/10.1080/10937404.2013.842523
DOI: 10.1016/j.cmet.2021.09.004

PESTICIDES

THE INVISIBLE GUT DISRUPTORS

Biocidin Botanicals™

PESTICIDES: AN AMERICAN EXPERIMENT

Front. Endocrinol. 7:30. doi: 10.3389/fendo.2016.00030

- According to the USDA, a total of about 400 different agricultural pesticides totaling >1 billion lbs. were used in the United States in 2017, the latest year data is available.
- 60% (> 645 million lbs.) were considered hazardous to human health, according to the WHO's data.
- 25 pesticides that are banned in more than 30 countries were still being used in the U.S. in 2017.
- Phorate, the most-used "extremely hazardous" insecticide in the U.S. in 2017, is banned in 38 countries including China, Brazil, and India.
- None of the "extremely hazardous" pesticides can be used in the 27 nations of the European Union.

https://water.usgs.gov/nawqa/pnsp/usage/maps/county-level/
https://www.who.int/publications/i/item/9789240005662

Organochlorine Pesticides

Environ Health Perspect, 2004, 112(2): 186-200.

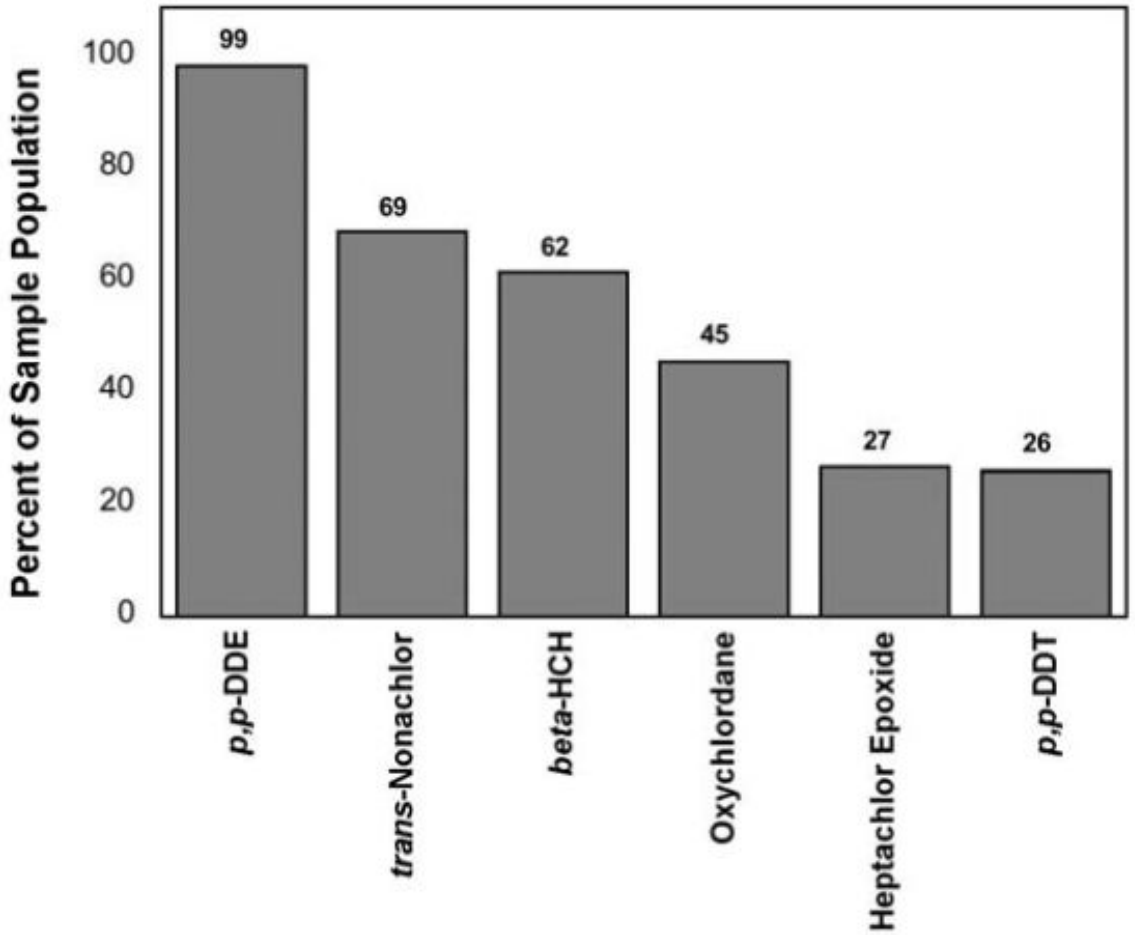


Figure 2. A High Percentage of Those Tested Had Pesticides or Metabolites in Blood. Three of the six organochlorine pesticides found in blood were present in more than 50% of the people whose blood was tested.

Organochlorine Pesticides

Environ Health Perspect, 2004, 112(2): 186-200.

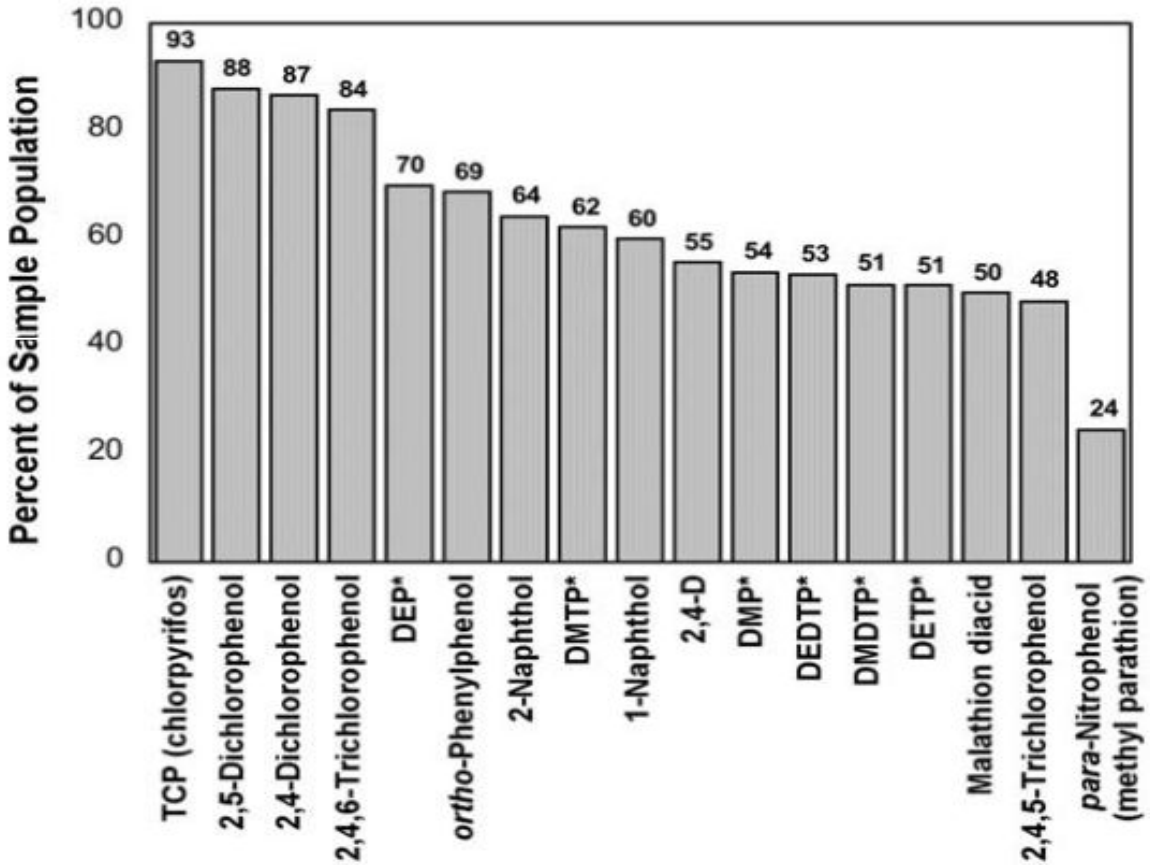


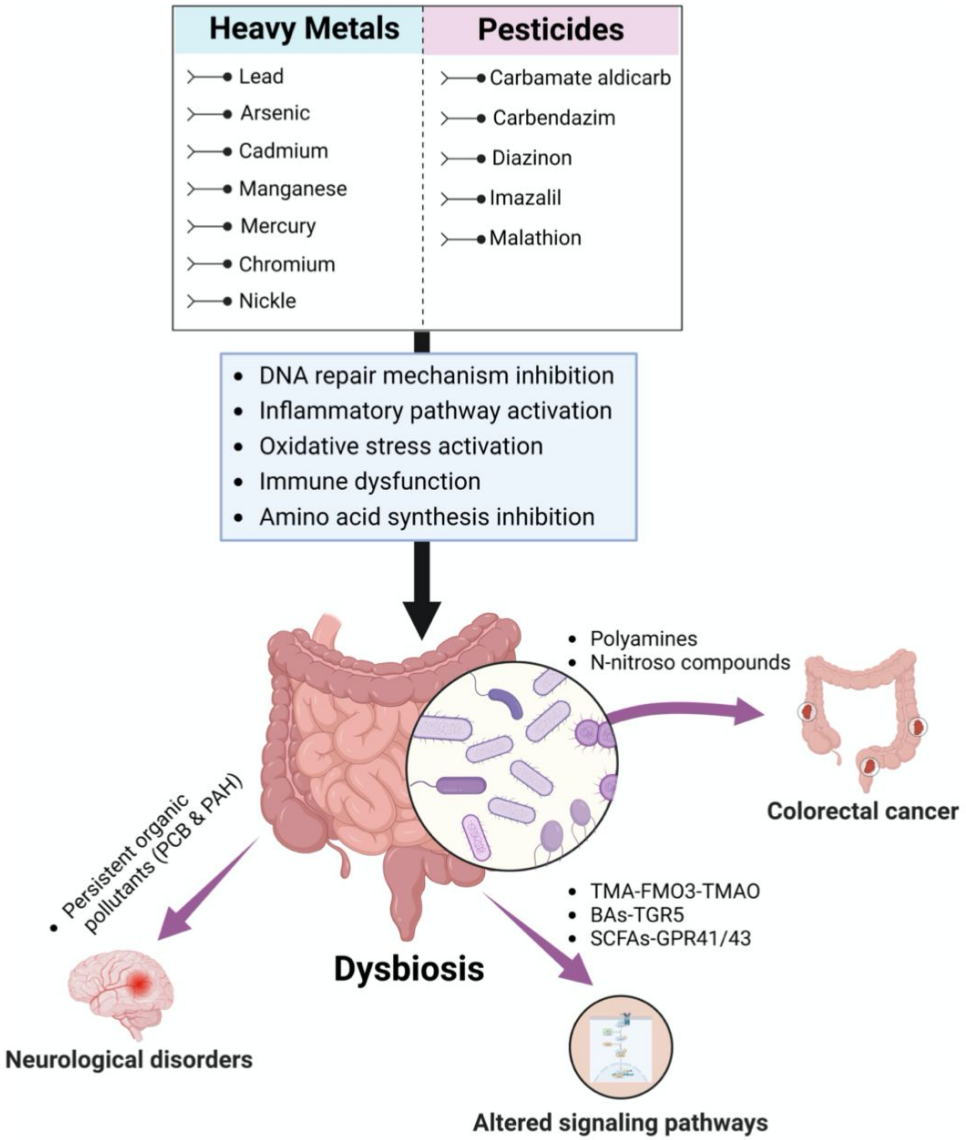
Figure 1. A High Percentage of Those Tested Had Pesticides or Metabolites in Urine. Fifteen of the pesticides or metabolites found in urine were present in 50% or more of people whose urine was tested.

CHILDREN ARE VULNERABLE

- Chlorpyrifos (Dursban, Lorsban, Brodan) – detected in over 90% of children's urine in 2010.
- Pyrethrin metabolite (3-BPA) in 60 – detected in 100% of children's urine.
- Diazinon (Spectracide) 77 – detected in 100% of children's urine.
- Analysis of NHANES subset: 1,139 children, age 8-15. Children with higher metabolite levels were significantly more likely to be diagnosed with ADHD than children with lower exposure.

Environ Health Perspect 2010;118:1768-74. Pediatrics 2010;125:e1270-7.

PESTICIDES AND METALS



https://doi.org/10.1080/19490976.2023.2187578

EFFECTS OF PESTICIDES ON GUT

European Journal of Nutrition
https://doi.org/10.1007/s00394-021-02548-6

REVIEW

Chronic oral exposure to pesticides and their consequences on metabolic regulation: role of the microbiota

Narimane Djekkoun[1] · Jean-Daniel Lalau[1,2] · Véronique Bach[1] · Flore Depeint[3] · Hafida Khorsi-Cauet[1]

Received: 16 December 2020 / Accepted: 22 March 2021

PMID: 33837455

One of the key effects on the microbiota is the reduced *Bacteroidetes* and increased *Firmicutes* phyla, reflecting both pesticide exposure and risk factors of dysmetabolism.

Dysbiosis leading to endotoxemia, mucosal permeability, and LPS to bacterial translocation. Low-grade inflammation has also been shown for a number of pesticides.

PESTICIDES THAT CAUSE DYSBIOSIS

Dysbiosis affecting the distribution of *Bacteroidetes* to *Firmicutes:*

- **DDT**
- **Carbendazim**
- **Diazinon**
- **2,3,7,8-tetrachlorodibenzofuran** (East Palestine train derailment combustion product)

Permethrin (common indoor and outdoor pesticides)

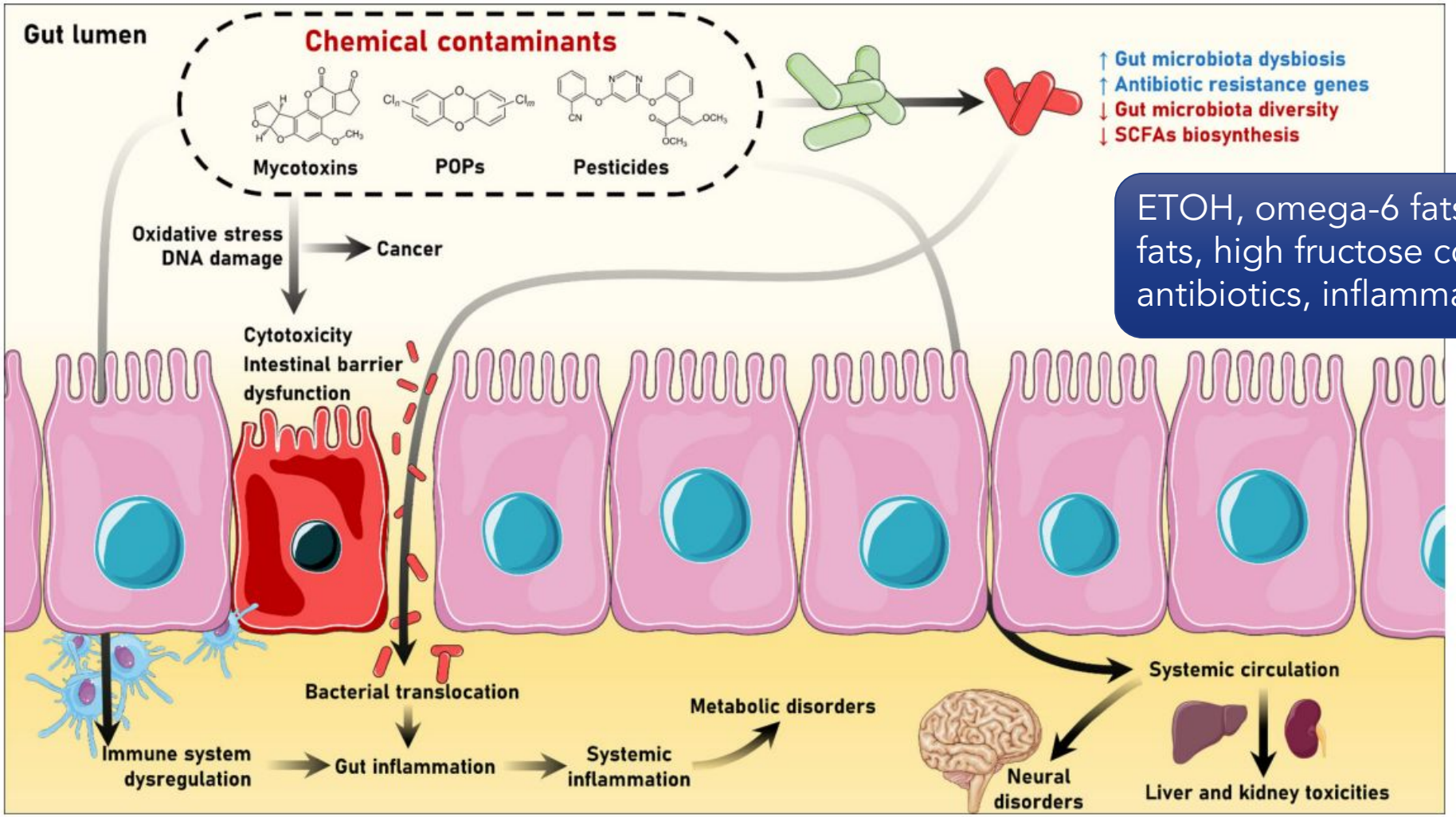
- Changes in acetic and propionic acid levels
- Reduced abundance of *Bacteroides-Prevotella-Porphyromonas* species; increased *Enterobacteriaceae* and *Lactobacillus*
- In-vitro showed higher antibacterial activity against beneficial bacteria such as *Bifidobacterium* and *Lactobacillus paracasei*

Glyphosate

- Rats fed with 5, 50, and 500 mg/kg b.w. of glyphosate for 35 consecutive days showed intestinal inflammation and dramatically decreased relative abundance of the phylum *Firmicutes* and the genus *Lactobacillus*
- Several potentially pathogenic bacteria were increased

PMID: 33837455

WHEN DISEASE STARTS IN THE GUT



ETOH, omega-6 fats, saturated fats, high fructose corn syrup, antibiotics, inflammation

PMID: 33063532

https://youtu.be/-QrrlqAeM2I

DYSBIOSIS PATTERNS

Dysbiosis affecting the distribution of *Bacteroidetes* to *Firmicutes:*

- DDT
- Carbendazim
- Diazinon
- 2,3,7,8-tetrachlorodibenzofuran
- DDT

Permethrin

- Changes in acetic and propionic acid levels
- Reduced abundance of *Bacteroides-Prevotella-Porphyromonas* species; increased *Enterobacteriaceae* and *Lactobacillus*
- In-vitro showed higher antibacterial activity against beneficial bacteria such as *Bifidobacterium* and *Lactobacillus paracasei*

PMID: 33837455

CHLORPYRIFOS

Foods With Chlorpyrifos Residue

What Food?	Average Level (µg/kg)[1,2]	Maximum Level (µg/kg)[3]	Details on How Much	Test Year[4]
Apples-Single Servings	12.4	540.0	Show More Details	1999
Sweet Bell Peppers	10.9	360.0	Show More Details	2012
Cranberries	5.7	93.0	Show More Details	2006
Greens, Kale	5.1	1100.0	Show More Details	2008
Cilantro	4.1	670.0	Show More Details	2010
Asparagus	3.2	320.0	Show More Details	2010
Hot Peppers	2.7	200.0	Show More Details	2011

Simulated Human Microbial Ecosystem Model (SHIME) inoculated with healthy human feces for 60 days.

Exposure to CPF: microbial dysbiosis associated with proliferation of *Enterobacteriaceae*, *Bacteroides* spp. and decreased levels of *Lactobacillus* spp. and *Bifidobacterium* spp.

At the genus level, around 25 genera of bacteria in the gut changed significantly.

https://www.whatsonmyfood.org/pesticide.jsp?pesticide=160

PMID: 33837455

Liang *et al. Microbiome* (2019) 7:19
https://doi.org/10.1186/s40168-019-0635-4

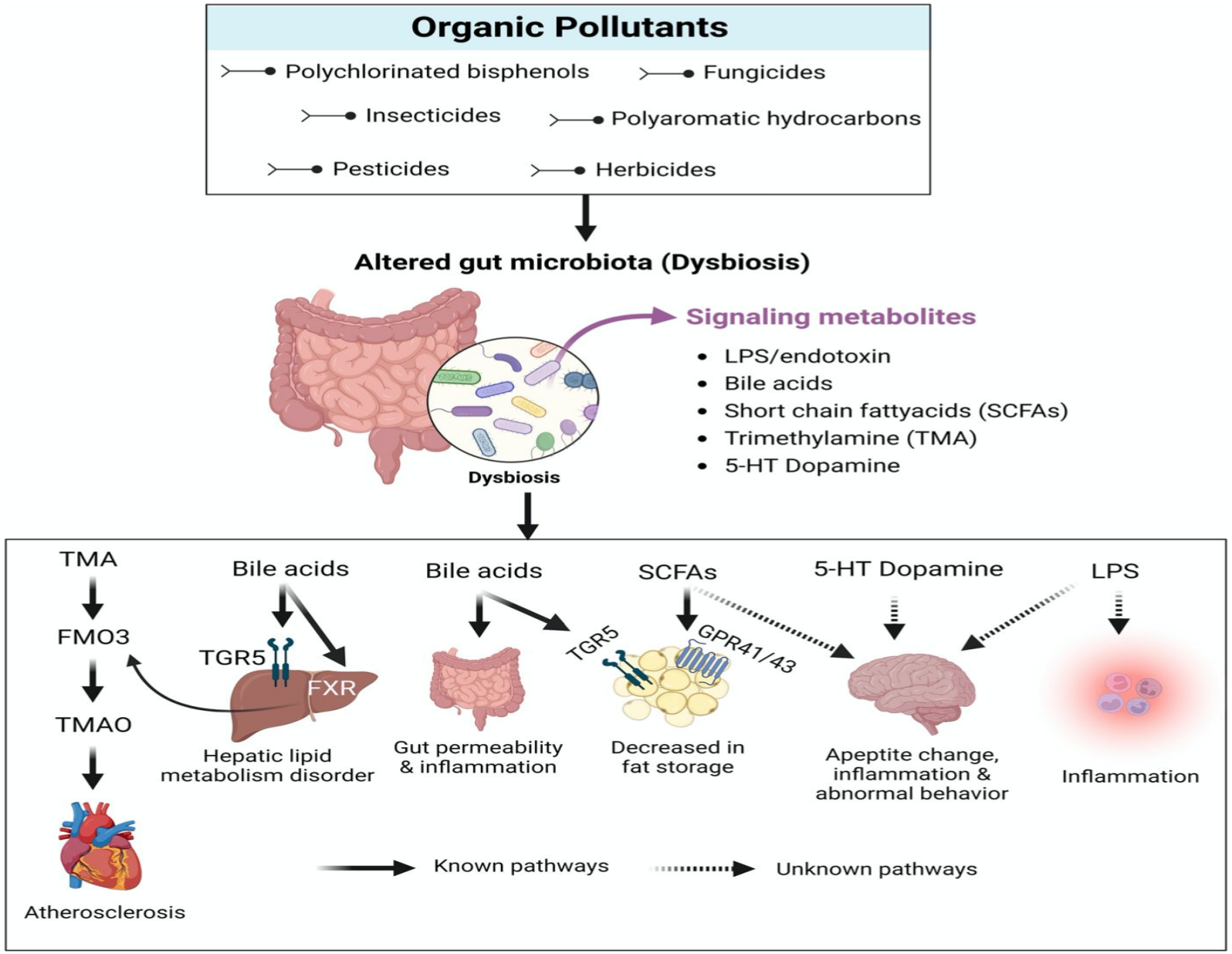
Microbiome

RESEARCH Open Access

Organophosphorus pesticide chlorpyrifos intake promotes obesity and insulin resistance through impacting gut and gut microbiota

Yiran Liang[1,2†], Jing Zhan[1†], Donghui Liu[1], Mai Luo[1], Jiajun Han[1], Xueke Liu[1], Chang Liu[1], Zheng Cheng[1], Zhiqiang Zhou[1] and Peng Wang[1*]

"Chlorpyrifos caused broken integrity of the gut barrier, leading to increased lipopolysaccharide entry into the body and finally low-grade inflammation, while genetic background and diet pattern have limited influence on the chlorpyrifos-induced results. Moreover, the mice given chlorpyrifos-altered microbiota had gained more fat and lower insulin sensitivity."



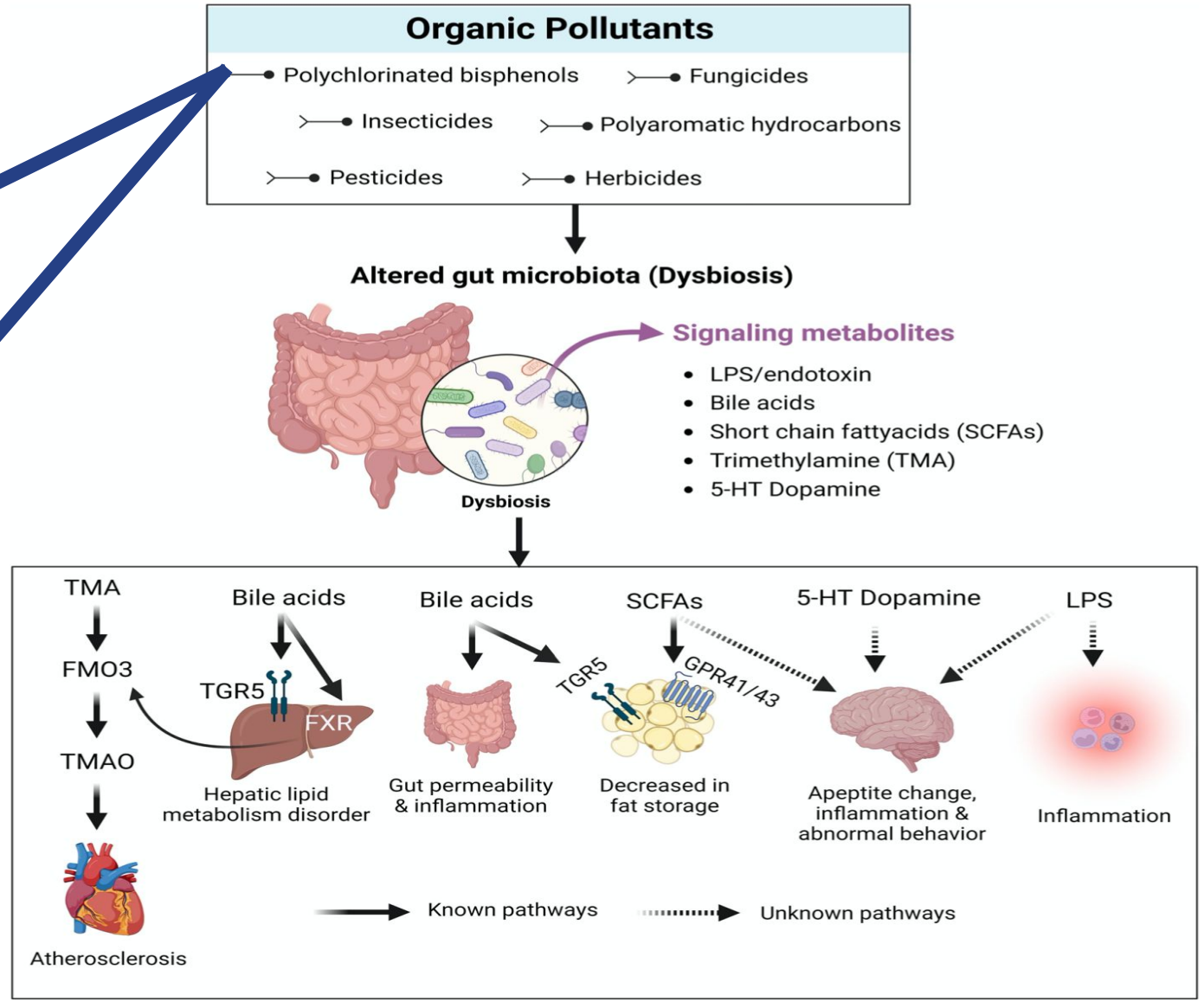
https://doi.org/10.1080/19490976.2023.2187578

Organochlorine pesticides cause

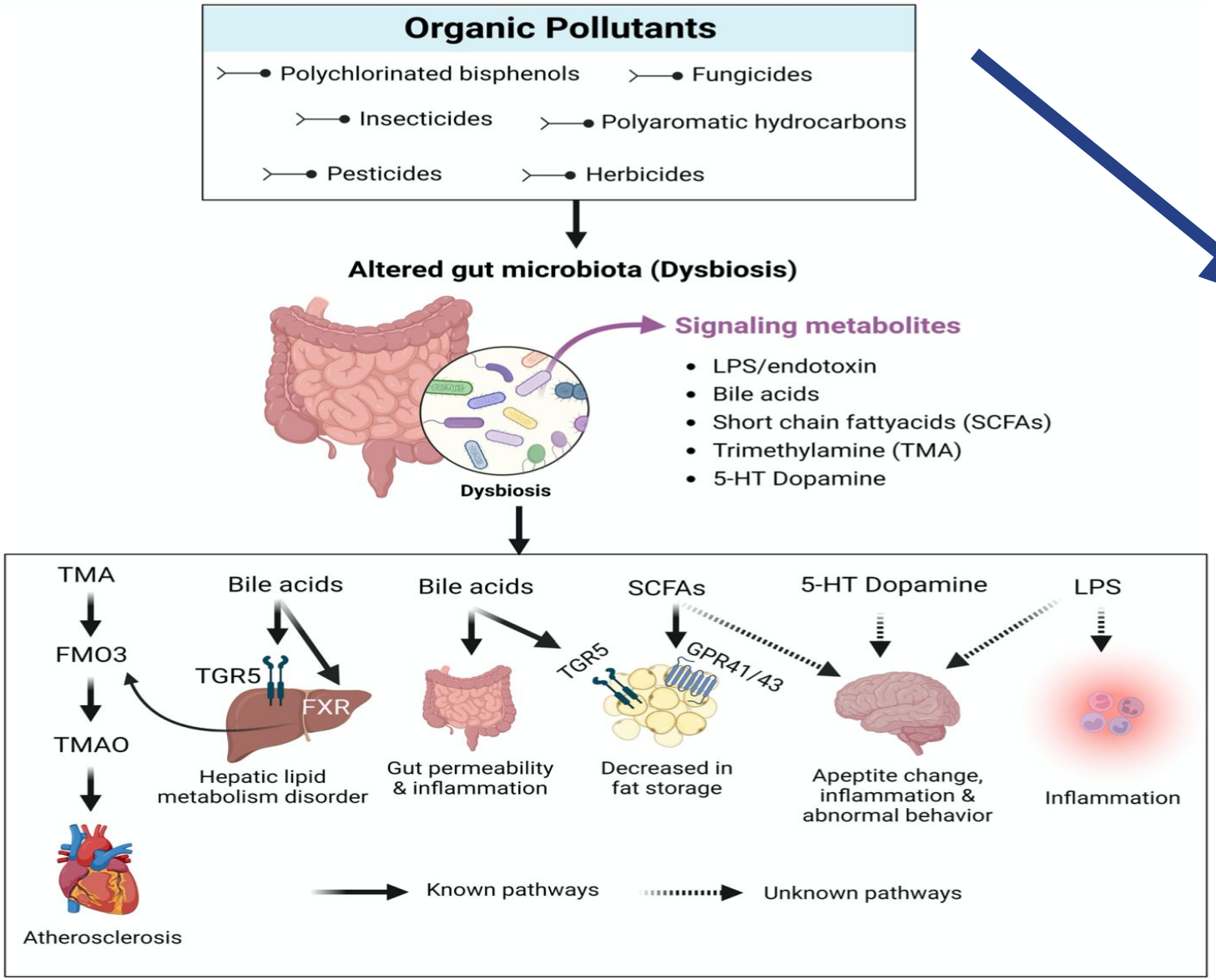
- increase methanobacteria and obesity
- alter bile acid synthesis and re-sorption and decrease microbiome diversity
- Increase quorum sensing, virulence, and pathogenicity

Organophosphate pesticides

- Plasma levels predict diabetes
- Gut microbial-mediated degradation
- OPP alters esterase activities acetate gluconeogenesis and glucose intolerance
- Chlorpyrifos/diazinon cause dysbiosis, induce glucose intolerance and lead to intestinal inflammation

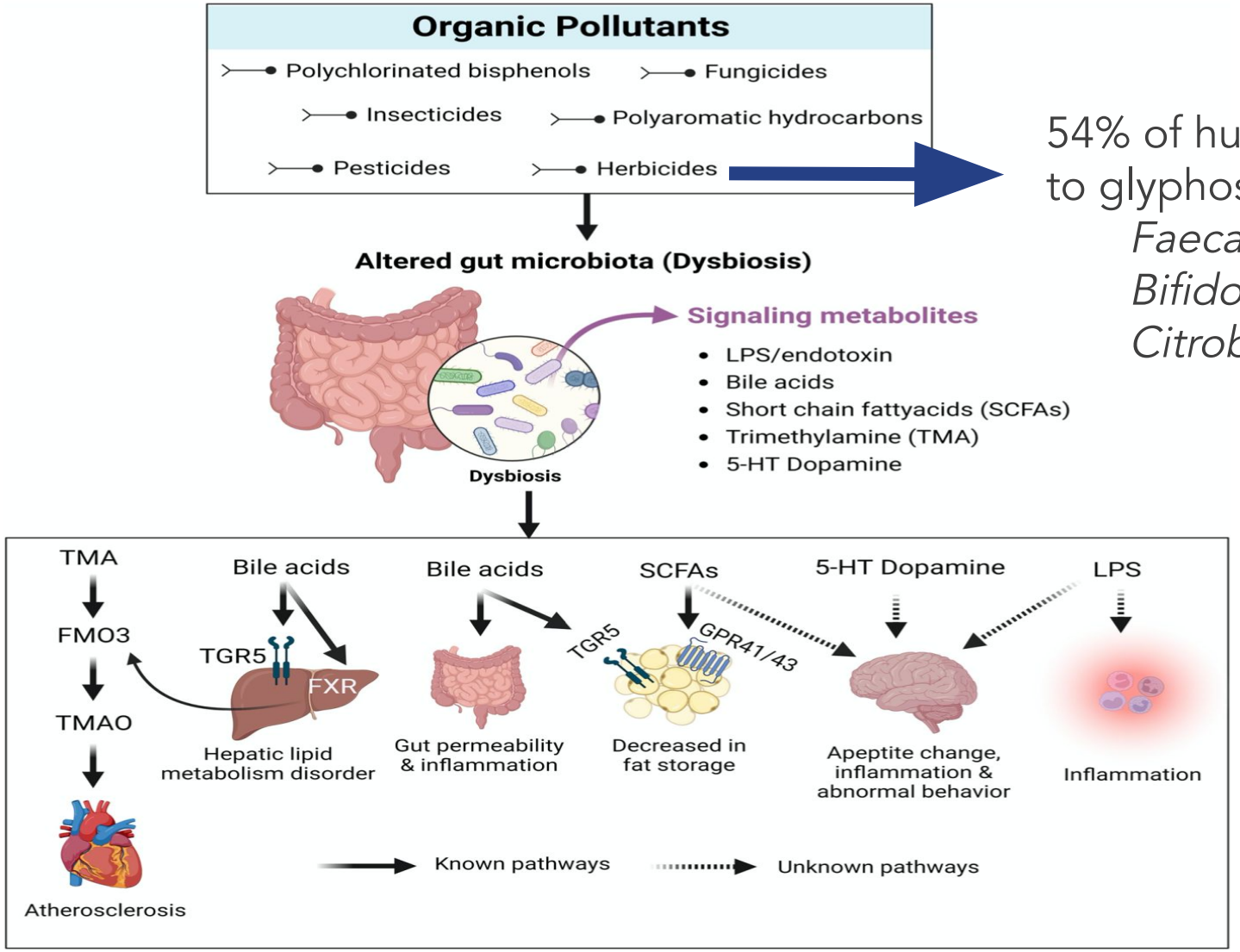


https://doi.org/10.1080/19490976.2023.2187578



Feeding in mice resulted in a damaged gut barrier, increased TMA, dyslipidemia, and increased intestinal absorption of triglycerides leading to increased inflammation.

https://doi.org/10.1080/19490976.2023.2187578



54% of human microbiome is sensitive to glyphosate:

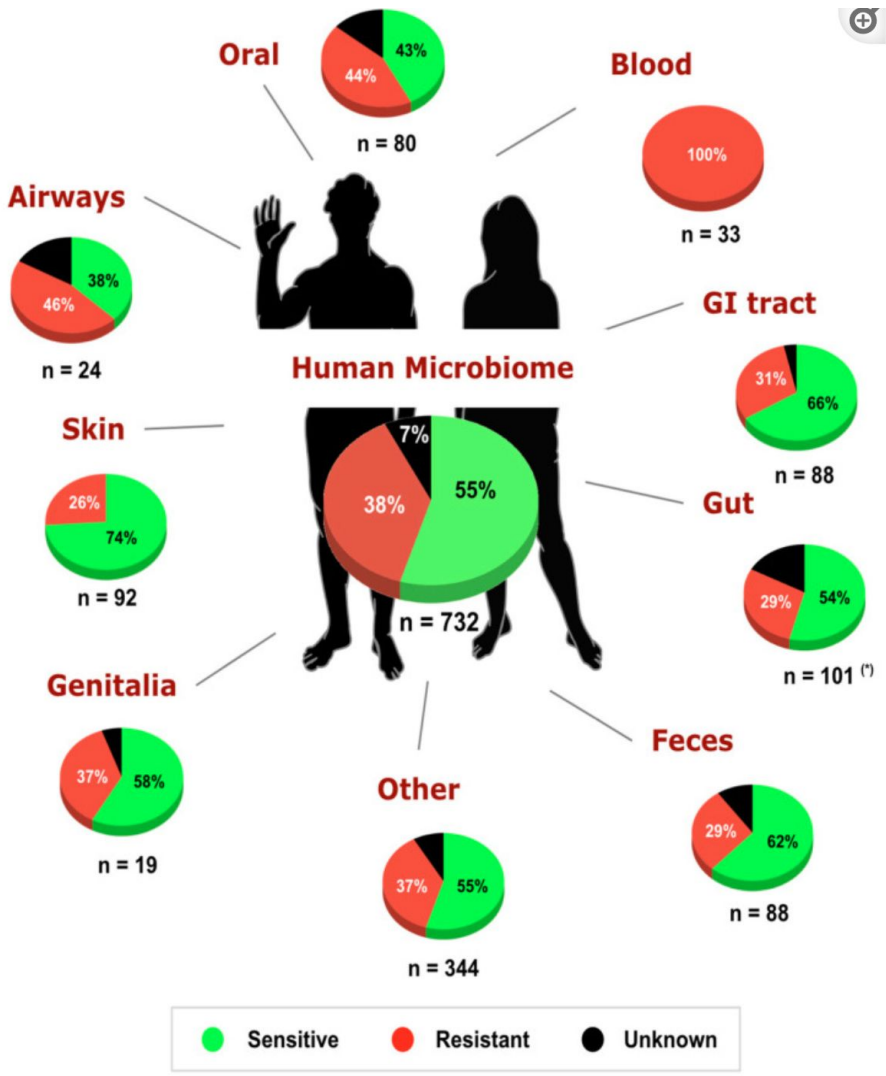
Faecalibacterium,
Bifidobacterium, and
Citrobacter

https://doi.org/10.1080/19490976.2023.2187578
doi: 10.3390/life12050707

The percentages of microbiota in green are those that use the shikimate pathway to survive. Those in red have developed resistance to glyphosate.

These microbiota can potentially be affected by glyphosate due to their vulnerability to the inactivation of the central enzyme 5-enolpyruvylshikimate-3-phosphate synthase (EPSPS), an almost universal enzyme in plants, fungi, and prokaryotes, for the synthesis of three aromatic amino acids.

Bacteria with sensitive copies of the EPSPS enzyme include:
Faecalibacterium,*Bifidobacterium*,
and *Citrobacter*. *Clostridium*,
Dorea, and *Ruminococcus* mostly have resistant sequences. These genera have previously been associated with irritable bowel syndrome.



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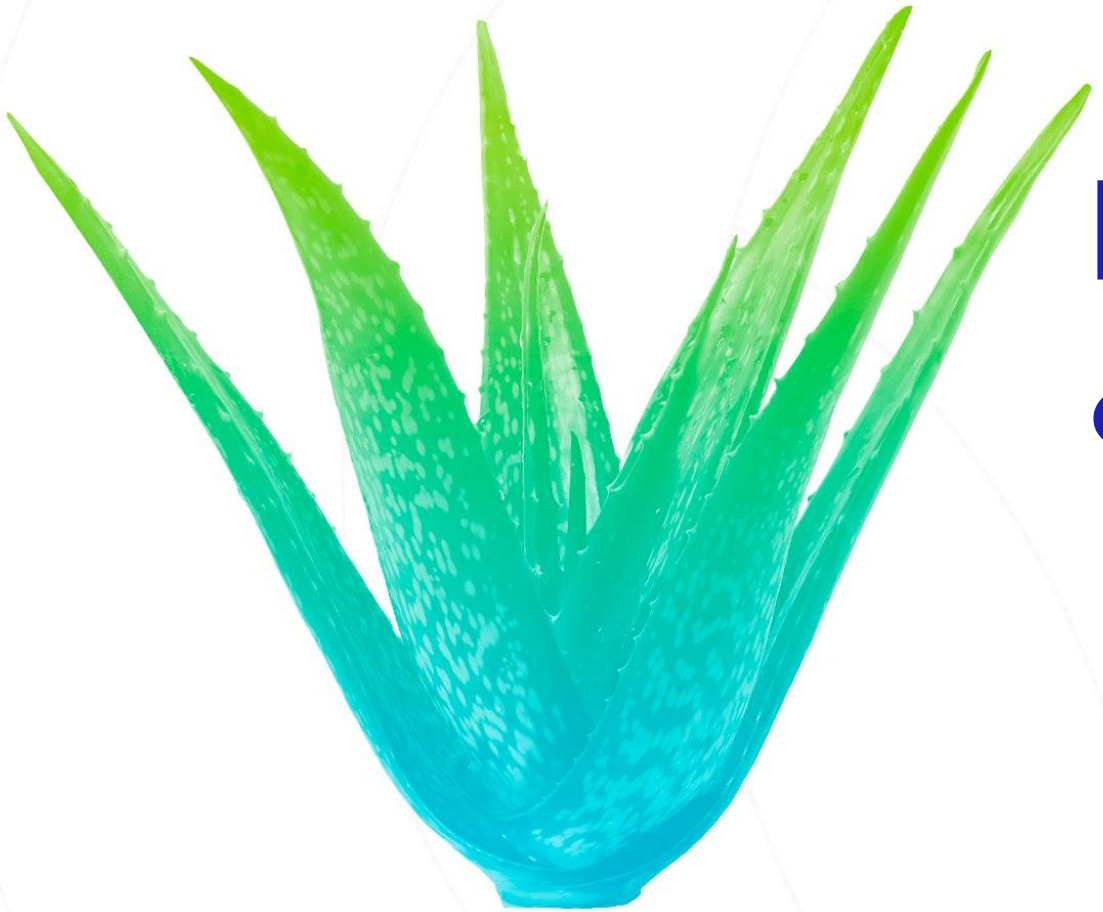


POPS: PCBS & PAHS

PERSISTENT ORGANIC POLLUTANTS: POLYCHLORINATED BIPHENYLS AND POLYAROMATIC HYDROCARBONS

THE POPS (PERSISTENT ORGANIC POLLUTANTS)

PCBs (polychlorinated biphenyls):

- Found in OVER 90% of adults and children tested by CDC in the U.S.
- Stored in adipose and tissue
- Persistent means it takes up to six decades to eliminate them from the body

PAHs (Polyaromatic hydrocarbons):

- Found in urban air, cigarette smoke, wood smoke (forest fires), grilled meat or food, dyes, plastics (house fires), pesticides, and parking lots or roofs sealed with coal tar sealant
- Living near a Superfund Site or hazardous waste site
- Bivalve species such as mussels, clams, and oysters readily accumulate PAHs
- In fatty tissue, the concentrations can become magnified by up to 70,000 times higher than the background levels
- Can induce intestinal inflammation, ileal lesions, and shifts gut microbiota populations

PMID: 30373033
PMID: 27503127

PCBS AND ENDOCRINE DISRUPTING EFFECTS

- PCBs – Chlorinated industrial compounds a family of chemicals
- Sources: Was used as machine lubricant, power line component, found in transformers. Banned since late 70's but a Persistent Organic Pollutant. Now found in fatty animals, dairy, eggs, and fish – especially farmed salmon
- Effects: Neurotoxin • Immune toxin • Reproductive toxin • Endocrine disruptor • Teratogenic • Carcinogenic • Strongly associated with Metabolic Syndrome • Obesity • Diabetes • Hypertension • Fatty liver • Autoimmune thyroiditis
- Half life: Months to 60 years. Sweat, stool, and breastfeeding are significant excretory pathways

https://www.atsdr.cdc.gov/csem/csem.asp?csem=30&po=10

LEVELS OF CONCERN

“There is no “safe” level of PCBs. All our research indicates that more is worse, but that even the level now commonly found in the average person increases risk of disease.”

– David Carpenter MD, MPH, Dean of the University at Albany School of Public Health. He contributed to 435 peer-reviewed publications, most of them on PCB toxicology and human research.

Watch a recent presentation by Dr.Carpenter explaining why Monsanto attacked his faculty position at University of Albany because he was acting as an expert witness in a class action lawsuit for PCB-poisoned Native tribe: https://youtu.be/-QrrlqAeM2I (starting at 33:59 in video)

25 YEARS LATER: STILL IN OUR FAT AND OUR CHILDREN'S FAT ... AND THEIR CHILDREN'S FAT

Serum 3,3',4,4',5-Pentachlorobiphenyl (PCB 126) (lipid adjusted) (1999 – 2004)

CAS Number 57465-28-8

Geometric mean and selected percentiles of serum concentrations (in pg/g lipid or parts per trillion on a lipid-weight basis) for the U.S. population from the National Health and Nutrition Examination Survey. See the following page for data from later NHANES Survey periods.

Categories (Survey Years)	Geometric Mean (95% conf. interval)	50th Percentile (95% conf. interval)	75th Percentile (95% conf. interval)	90th Percentile (95% conf. interval)	95th Percentile (95% conf. interval)	Sample Size
Total population (1999 - 2000)	*	< LOD	28.5 (24.9-32.8)	53.2 (45.7-59.9)	80.5 (62.8-100)	1896
Total population (2001 - 2002)	22.7 (20.9-24.7)	24.5 (22.2-26.8)	40.8 (36.1-47.5)	69.3 (61.6-80.8)	108 (92.7-116)	1226
Total population (2003 - 2004)	16.3 (14.9-17.9)	14.7 (<LOD-16.5)	24.8 (22.4-27.4)	46.7 (41.6-51.9)	68.7 (58.1-84.4)	1860
Age 12-19 years (1999 - 2000)	*	< LOD	< LOD	24.3 (<LOD-27.5)	31.1 (26.4-36.4)	658
Age 12-19 years (2001 - 2002)	†	†	†	†	†	†
Age 12-19 years (2003 - 2004)	*	< LOD	< LOD	17.0 (15.2-20.2)	21.2 (17.3-25.6)	577
Age 20+ years (1999 - 2000)	*	< LOD	30.8 (27.2-36.3)	57.1 (50.5-65.8)	89.5 (66.1-110)	1238
Age 20+ years (2001 - 2002)	22.7 (20.9-24.7)	24.5 (22.2-26.8)	40.8 (36.1-47.5)	69.3 (61.6-80.8)	108 (92.7-116)	1226
Age 20+ years (2003 - 2004)	17.6 (16.0-19.3)	16.0 (14.2-18.6)	26.8 (24.2-30.3)	49.8 (43.5-59.1)	74.8 (60.2-94.4)	1283

PCBS IN AROCLOR

Table III. Dioxin-like PCB Congener Concentrations in Commercial Aroclors*
(all concentrations in µg/g or ppm)

PCB Congener	WHO TEF	Aroclor 1221	Aroclor 1232	Aroclor 1016	Aroclor 1242	Aroclor 1248	Aroclor 1254	Aroclor 1260	Aroclor 1262	Aroclor 1268
77	0.0001	12.6	2150	40.9	2590	4440	174	33.8	84.6	36.1
81	0.0003	0.51	111	1.96	156	221	16.4	3.33	4.63	1.35
105	0.00003	55.9	3030	69.5	4840	17300	33800	434	764	107
114	0.00003	4.04	248	6.03	443	1320	1930	17	46	5.86
118	0.00003	88.1	4460	110	6980	24200	78900	5610	1980	101
123	0.00003	3.33	164	4.72	277	806	1150	5.02	27.8	3.24
126	0.1	0.28	21	0.56	33.6	98	37.3	2.13	2.28	1.76
156	0.00003	7.49	90.7	3.72	255	654	8440	4860	946	17.6
157	0.00003	1.46	22	1.03	70.9	171	1870	252	63.8	7.92
167	0.00003	2.52	32.4	1.1	80.7	207	3100	1990	278	4.96
169	0.03	0.08	0.17	0.13	0.11	0.21	0.81	0.82	0.4	0.32
189	0.0003	1.17	4.36	0.12	4.53	11	246	1290	451	4.4

SOURCES OF EXPOSURE

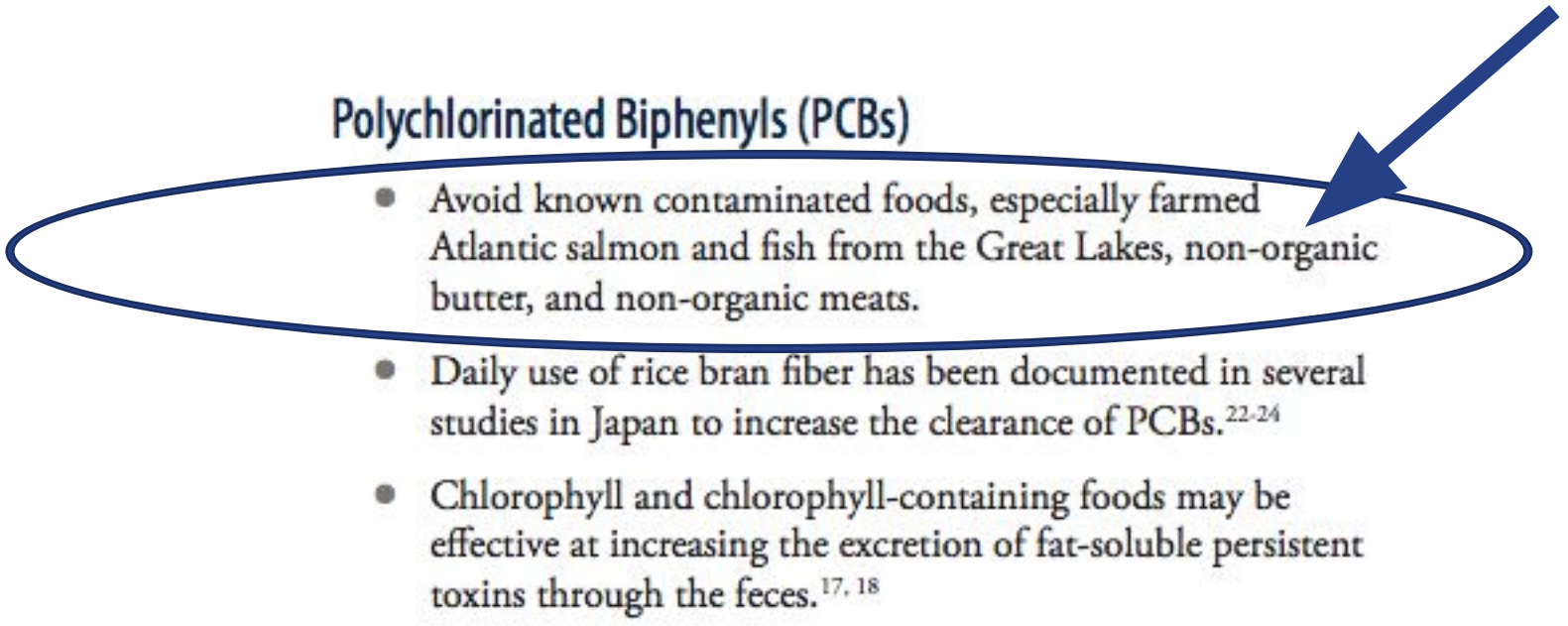
- There are two basic sources of exposure to PCBs. You can eat and drink them, OR breathe airborne PCBs that can also be absorbed through the skin.

- Dietary Sources: farmed fish, fish from Great Lakes including Chinook Salmon and bottom-feeding fish (catfish, buffalo, and carp), beef, dairy products, butter, cheese, mother's milk, canned sardines, fish oil.

Environ Health Perspect 118:796–802 (2010). doi:10.1289/ehp.0901347/*Environ Health Perspect*. 2013;121(3):A86-A93. doi:10.1289/ehp.121-a86

INACCURATE ADVICE

PCBs are volatile and airborne. They fall with precipitation and are found in soil, grass, river and lake bottoms. They may be eaten by free-range animals who forage and accumulate PCBs as a result.

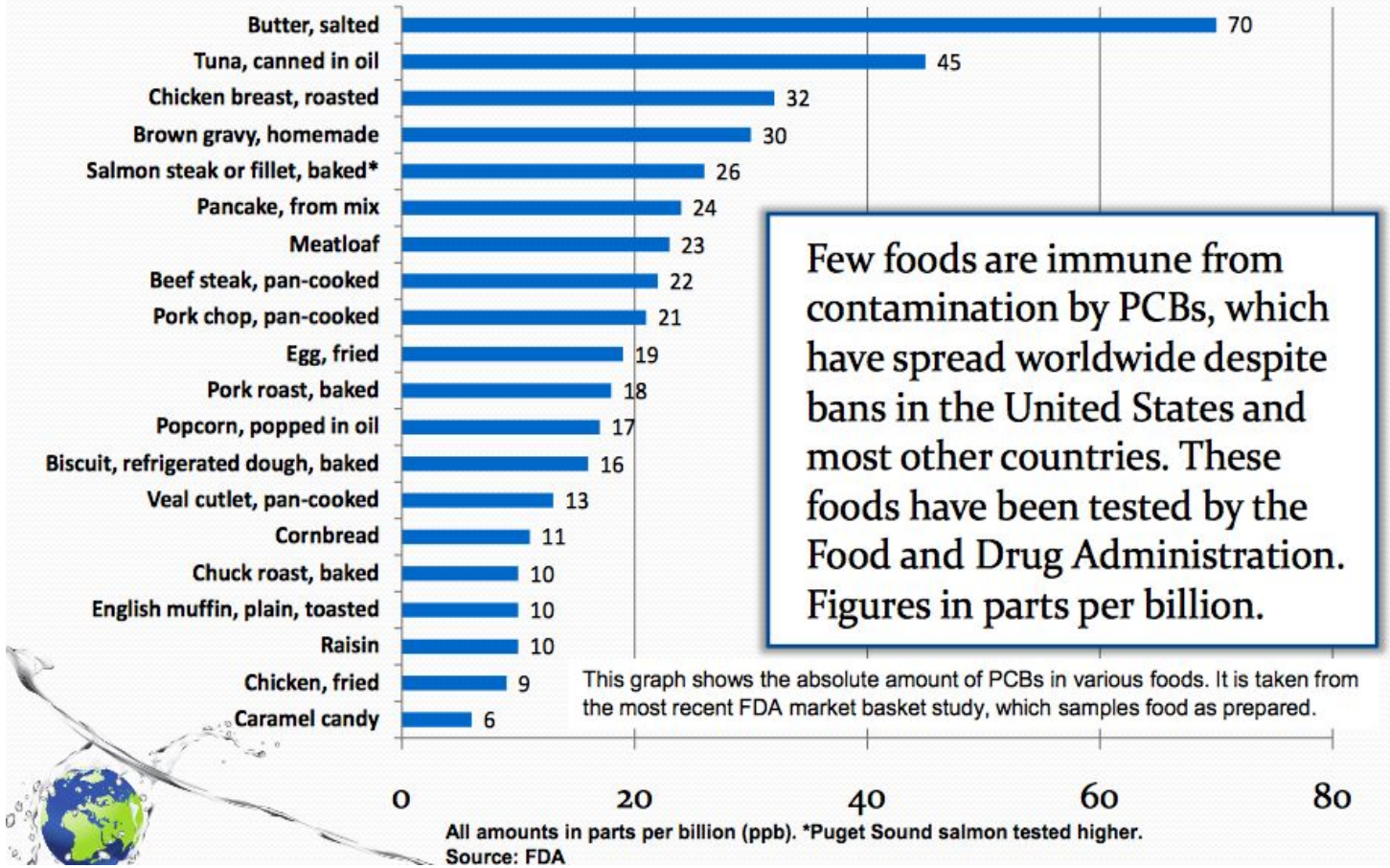


Polychlorinated Biphenyls (PCBs)

- Avoid known contaminated foods, especially farmed Atlantic salmon and fish from the Great Lakes, non-organic butter, and non-organic meats.
- Daily use of rice bran fiber has been documented in several studies in Japan to increase the clearance of PCBs.[22-24]
- Chlorophyll and chlorophyll-containing foods may be effective at increasing the excretion of fat-soluble persistent toxins through the feces.[17, 18]

Genova Labs Toxic Effects CORE Interpretive Guide pg. 9

PCB Levels in Other Foods



OTHER SOURCES OF EXPOSURE

- Air: PCBs volatilize from waste sites and can be inhaled or dermally absorbed. Since they are fat-soluble, they pass right through the skin.
- This is an issue in city air and the air of buildings that were constructed using PCBs in sealants, caulking, and other building materials.
- This includes "non-legacy PCBs," PCBs that are unintentionally formed as by-products during the manufacture of paints and dyes that are currently sold. These PCBs are "lower-chlorinated" congeners.
- Older fluorescent lights found in schools, offices, and homes may still contain transformers or ballasts that contain PCBs. If the ballasts fail, PCBs can leak out and contaminate exposed surfaces and the air. PCB levels measured in the air after a light ballast failure can be significant.

MONSANTO LAWSUIT FROM PCB EXPOSURE IN SCHOOLS OPENS THE DOOR FOR MORE LEGAL ACTION

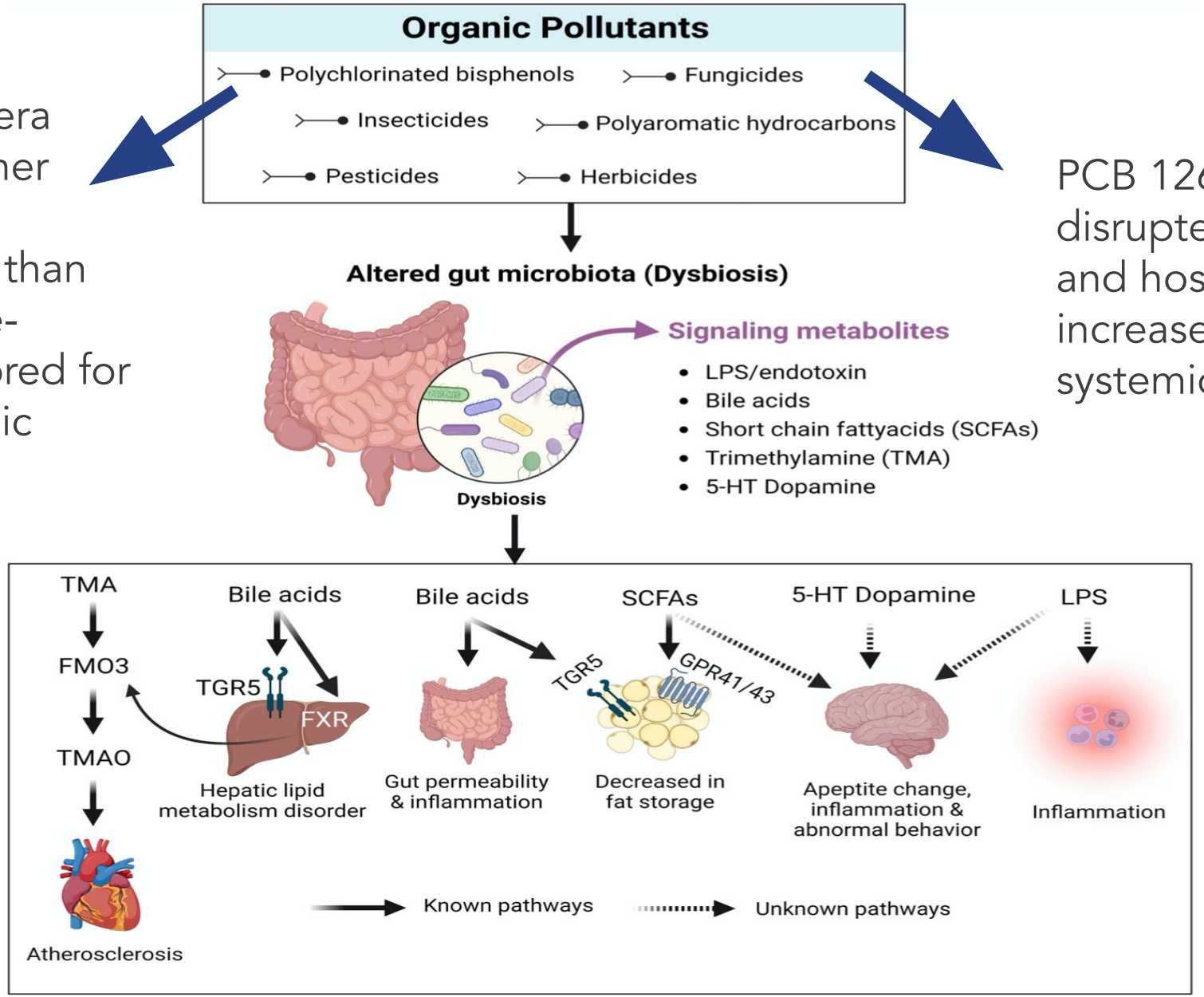
August 2021: Three teachers were awarded $185 million in lawsuit against Monsanto for PCB exposure resulting in brain damage.

Report from U.S. Senator Edward Markey shows: "up to 14 million students nationwide, representing nearly 30% of the school-aged population, may be exposed to PCBs in their schools, based on the estimated number of schools built during that time and how much PCB-containing material was used in these schools. A 2016 Harvard School of Public Health study estimates that between 12,960 and 25,920 schools have PCB-containing caulk."

The exposure is airborne from PCBs released from fluorescent light ballasts and caulk used up until 1979 when PCBs were outlawed due to their carcinogenicity. There are 12 suspected PCBs to measure found in all Aroclor (tradename for PCB products used in construction) attached here.

https://www.enjuris.com/blog/news/monsanto-pcb-verdict/
https://friedmanrubin.com/sky-valley/

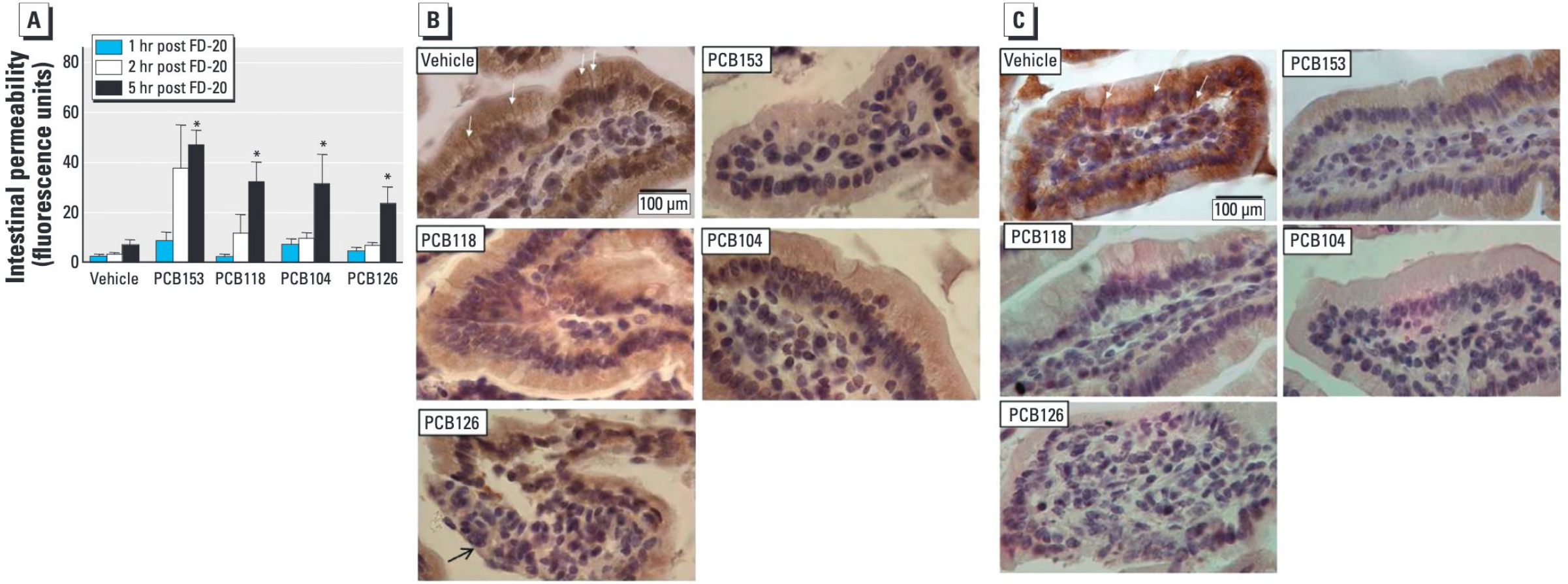
Clostridia genera was 420% higher among PCB-exposed mice than among vehicle-treated mice bred for cardiometabolic disease.



PCB 126 exposure in mice disrupted the gut microbiota and host metabolism and increased intestinal and systemic inflammation.

https://doi.org/10.1080/19490976.2023.2187578

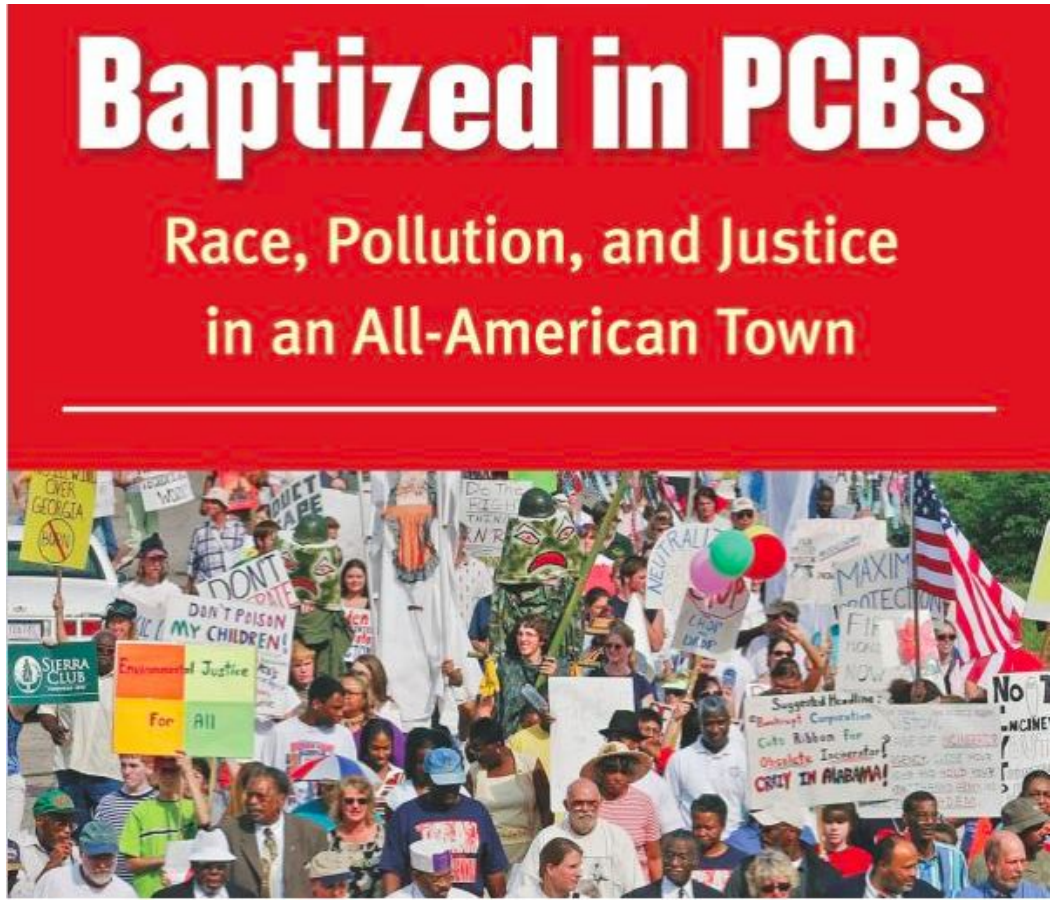
EFFECT OF PCB ORAL GAVAGE IN C57BL/6 MICE



PCB126 markedly disrupted the morphology of villi, as indicated by loss of the villus epithelium (B; black arrow)

PMID: 23632211/PMID: 20299304

ANNISTON, ALABAMA AND MONSANTO: THE LARGEST COHORT OF CHEMICALLY-INDUCED NAFLD IN THE WORLD?



Aroclor PCB mixtures were produced commercially from 1935 to 1971 in Anniston, Alabama. Chemical releases resulted in PCB contamination of soil, groundwater, and the blood/adipose tissue of residents.

PCBs are persistent organic pollutants with a half-life of up to 21-133 years for Aroclor mixtures. (ATSDR)
Anniston residents in the ACHS had 2-3 times higher mean PCB levels compared with NHANES cohort.

OXFORD
SOT | Society of Toxicology
www.toxsci.oxfordjournals.org
ToxSci 20 Years

TOXICOLOGICAL SCIENCES, 164(1), 2018, 39–49

doi: 10.1093/toxsci/kfy076
Advance Access Publication Date: April 19, 2018
Research Article

Liver Disease in a Residential Cohort With Elevated Polychlorinated Biphenyl Exposures

Heather B. Clair,[*] Christina M. Pinkston,[†,‡,§] Shesh N. Rai,[†,‡,§] Marian Pavuk,[¶] Nina D. Dutton,[‖] Guy N. Brock,[†] Russell A. Prough,[*] Keith Cameron Falkner,[§,‖,‖‖] Craig J. McClain,[§,‖,‖‖,#,**,††] and Matthew C. Cave[*,§,‖,‖‖,#,**,††,1]

TASH (toxicant-associated steatohepatitis) = environmental exposure- related liver disease characterized by hepatocellular necrosis, disrupted intermediary metabolism, and liver inflammation.

The difference between TASH and NASH/ASH: Primarily necrosis in TASH and apoptosis in ASH/NASH.

PMID: 29684222

ANNISTON, ALABAMA COMMUNITY HEALTH SURVEY: GROUND ZERO FOR PCBS

- Prevalence for obesity – 54%
- Prevalence for diabetes and high blood lipids – 27% both are directly correlated with blood levels of PCBs.
- Prevalence for liver disease – 60.2% among the highest ever reported for a residential cohort.
- 80.7% of those with liver disease have TASH

“NON-PERSISTENT” POLLUTANTS: BPA & TRICLOSAN

HIDDEN IN PLAIN SIGHT

Biocidin Botanicals™

TRICLOSAN: ANTIMICROBIAL PESTICIDE

- Antimicrobial in deodorants, toothpaste, shaving cream, mouthwash, cleaning supplies, grapefruit seed extract, detergents, skin cleansers, deodorants, lotions, creams, and dishwashing liquids.

- Urinary levels are positively associated with allergy, hay fever in those < 18, and IgE food antigenic sensitization in children. Measurable levels of TCS are present in milk and blood of nursing mothers.

- Elevated risk for MRSA formation in cell culture, endocrine disruption in animals (thyroid, sex hormone) mitochondrial toxicant, risk for contact dermatitis. Used in clothing as Microban.

J Allergy Clin Immunol. 2012 Aug;130(2):453-60.
Environ Health Perspect 2011;119(3):390-396.
PMID: 10399191 PMID: 10399191

TRICLOSAN: UNIVERSAL BIOCIDE

- Found in 97% of breast milk samples
- 75% of American urine sampled
- 47% of cord blood
- 58% of water bodies (rivers/streams)
- 43% liquid hand soap
- Removed from OTC hand sanitizers in 2017 for lack of safety data
- In 140 types of consumer products and clothing as MICROBAN
- Not required to be tested in tap water

Food Chem Toxicol 2007;45(1):125-9./Environ Health Perspect 2008;116(3): 303-307

TRICLOSAN: ANTIMICROBIAL PESTICIDE

- TCS is a selective inhibitor of phase II enzymes during glucuronidation and sulfonation of phenolic xenobiotics.
- Interferes with steroid hormone metabolism (PXR).
- Health problems connected to TCS include increased risks of allergies and asthma, altered immune responses, disruption of endocrine functions, and increased development of antibiotic resistance, esp MRSA.
- The application of biosolids is a common farming practice and a potential source of environmental exposure to triclosan as it has been measured in wastewater treatment plant effluent.

PMID: 29182464

MICROBIOME CAUSES METABOLIC ACTIVATION OF TRICLOSAN IN THE COLON & DRIVES GUT TOXICOLOGY

ARTICLE

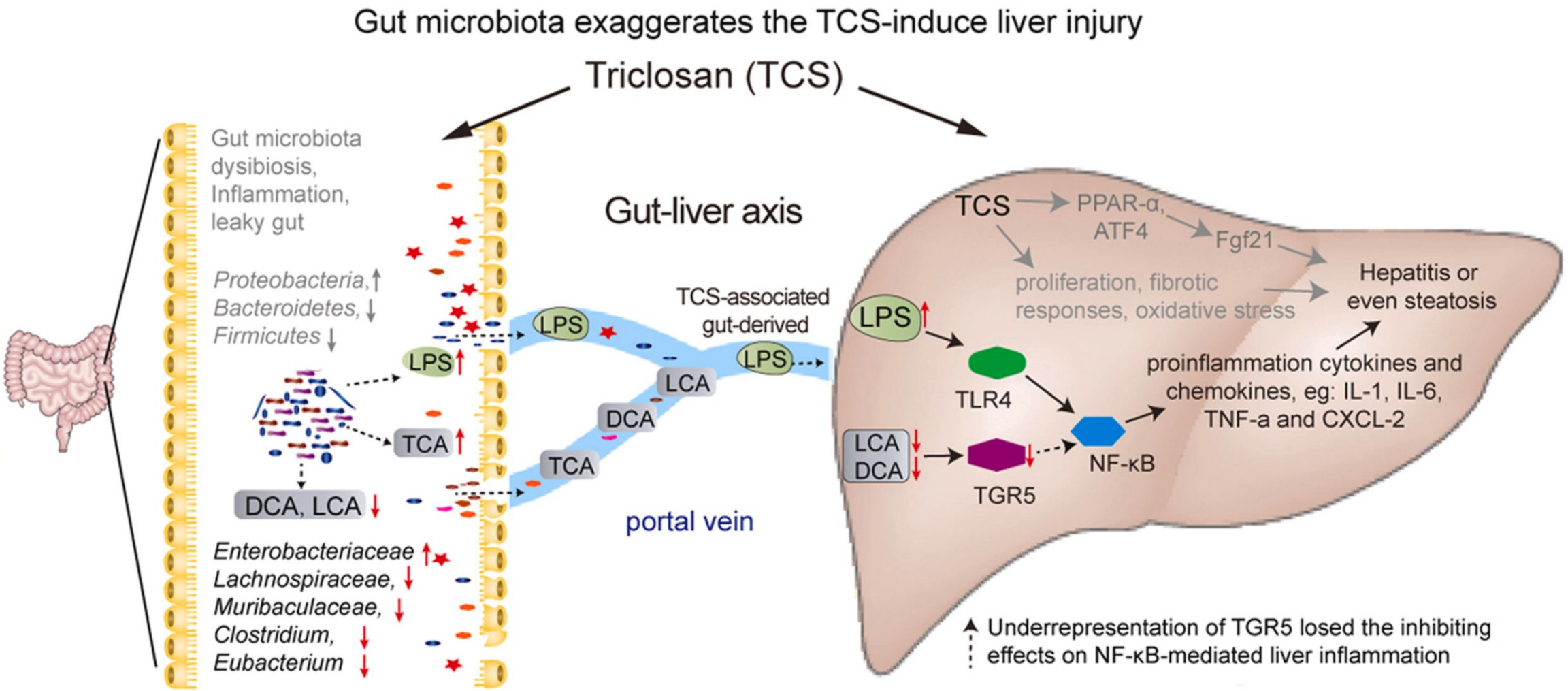
https://doi.org/10.1038/s41467-021-27762-y OPEN

Check for updates

Microbial enzymes induce colitis by reactivating triclosan in the mouse gastrointestinal tract

- TRICLOSAN has been shown to exacerbates colitis and colitis-associated colorectal tumorigenesis
- Commensal microbes generate specific microbial β-glucuronidase (GUS) Enzymes activate TCS-glucuronide (metabolically inactive) to triclosan where it can damage gut and lead to gut inflammation and dysbiosis

PMID: 35013263



PMID: 34315018

BISPHENOL A, ETC.

- More than 90% of the U.S. population revealed detectable BPA in their urine.
- The primary cause of exposure to BPA is canned food and beverages due to leakage from the protective lining, followed by the second largest source which is thermal paper used in all cash register receipts.
- Receipt paper marketed as BPA-free uses BPS instead, another known endocrine disrupting chemical.

European Food Safety Authority (EFSA) Parma 2015.

CURRENT SOURCES OF BISPHENOLS

- BPA: Polycarbonate plastics and epoxy resins, meat and seafood packaged in plastic, fast food (hamburgers)
- Bisphenol S (BPS): Food packaging – lining food cans, beverage containers
- Bisphenol F (BPF): Plastic dinnerware, dental sealants, thermal receipts
- Hidden bisphenols: Vinyl shower curtains, pillow protectors, dish and laundry detergents, tub and tile cleaners, soaps, lotions, shampoo, conditioner, shaving cream, nail polish, sunscreen
- Many other bisphenol analogues, including bisphenol AF (BPAF), bisphenol AP (BPAP), bisphenol Z (BPZ), and bisphenol B (BPB) have also been shown to exert estrogenic activities.

PMID: 31144713 PMID: 22398195

MORE ON BISPHENOL A (AND OTHERS)

December 15, 2021 – EFSA (European Food Safety Authority, equivalent of FDA in U.S.):

"... Re-evaluation of the risks to public health related to the presence of bisphenol A (BPA) in foodstuffs."

"Exposure to BPA through food and water above .04 ng per kg body weight is an unacceptably high exposure to BPA in the European Union."

The average exposure in the U.S. to children and adults over 2 years old is 200 ng per kg body weight – 5,000 times higher than .04 ng/kg body weight.

https://www.efsa.europa.eu/en/news/bisphenol-efsa-draft-opinion-proposes-lowering-tolerable-daily-intake

BPA IMMUNOTOXICITY

- EFSA review found clear evidence of harm for all human systems. They did find clear evidence for neurotoxicity, reproductive toxicity for both males and females, and immunotoxicity, especially for the effect on **Th17 cell dysregulation** which is correlated with allergies, asthma, and autoimmunity.

- EFSA identified the immune system as the **“most sensitive health outcome category,”** meaning that the immunotoxicity of BPA outweighed all other effects.

BPA AND IMMUNOTOXICITY

BPA exposure alters:

- T cell subsets
- B cell, dendritic cell, and macrophage function
- Upregulation of pro-inflammatory cytokines such as interferon-gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), IL-10, and IL-4
- Decreases T regulatory (Treg) cells
- Contributes to upregulation of TNF-α, IL-1β, IL-6, IL-8, and IL-2 (leading to cytokine storm)

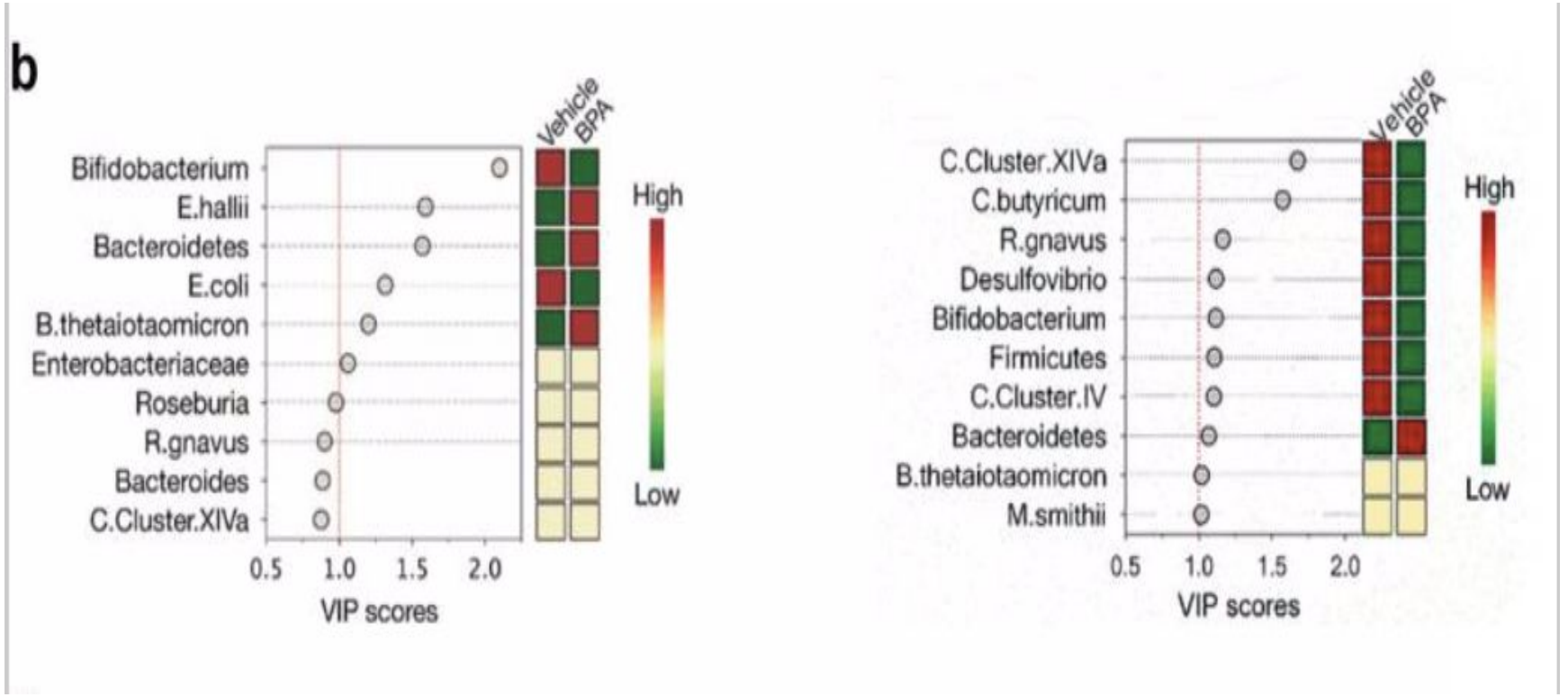
PMID: 23123408

ENDOCRINE DISRUPTING CHEMICAL
BPA CAUSES GUT DAMAGE

- BPA intake in mice led to a similar gut microbial community structure as that induced by high fat diet and high sugar diet in mice. (High fat diet in mice consists of 40% refined vegetable oil and 40% sugar)
- At levels equal to human exposure (4 mg/kg bw) mice fed BPA had increased markers of allergy to wheat and intestinal permeability, gut dysbiosis and decreased microbial diversity.
- BPA reduced microbiota metabolites derived from aromatic amino acids in the colon- associated with increased colonic inflammation and inflammatory bowel disease in animal model.

PMID: 27554980 PMID: 35567931 PMID: 32540565 PMID: 35780999 PMID: 35887390 PMID: 35430321
PMID: 29874946 PMID: 29101397

BPA CAUSES DYSBIOSIS



PERINATAL EXPOSURE TO BPA FOLLOWED THROUGH EARLY ADULTHOOD (DAY 45) TO OLD AGE (DAY 170)

PMID: 29101397

MOLD AND MYCOTOXINS

NEGATIVE HEALTH EFFECTS OF MOLDS AND FUNGUS

- Mold and fungal allergy or hypersensitivity reactions – IgE, IgG
- Consequences of ingestion of molds and mycotoxins
  - Alimentary Toxic Aleukia
  - Environmental Enteropathy
  - Mycotoxicoses (illness due to mycotoxins)
- Environmentally Acquired Illness (CIRS – Chronic Inflammatory Response Syndrome)
- Mycobiome and fungal biofilms
- Systemic mycoses – fungal infections

MYCOTOXINS: WHAT DO THEY REALLY DO?

Hepatotoxic – aflatoxin A
Nephrotoxic – ochratoxin A
Hematotoxic
Genotoxic
Estrogenic – zearalenone
Dermatotoxic
Teratogenic – aflatoxin A

Carcinogenic – ochratoxin A, aflatoxin A
Immunotoxic – ochratoxin A, gliotoxin
Cytotoxic – all of them
Neurotoxic – ochratoxin A, aflatoxin A
Gut-damaging – deoxynivalenol (main trichothecene)
Estrogenic – zearalenone

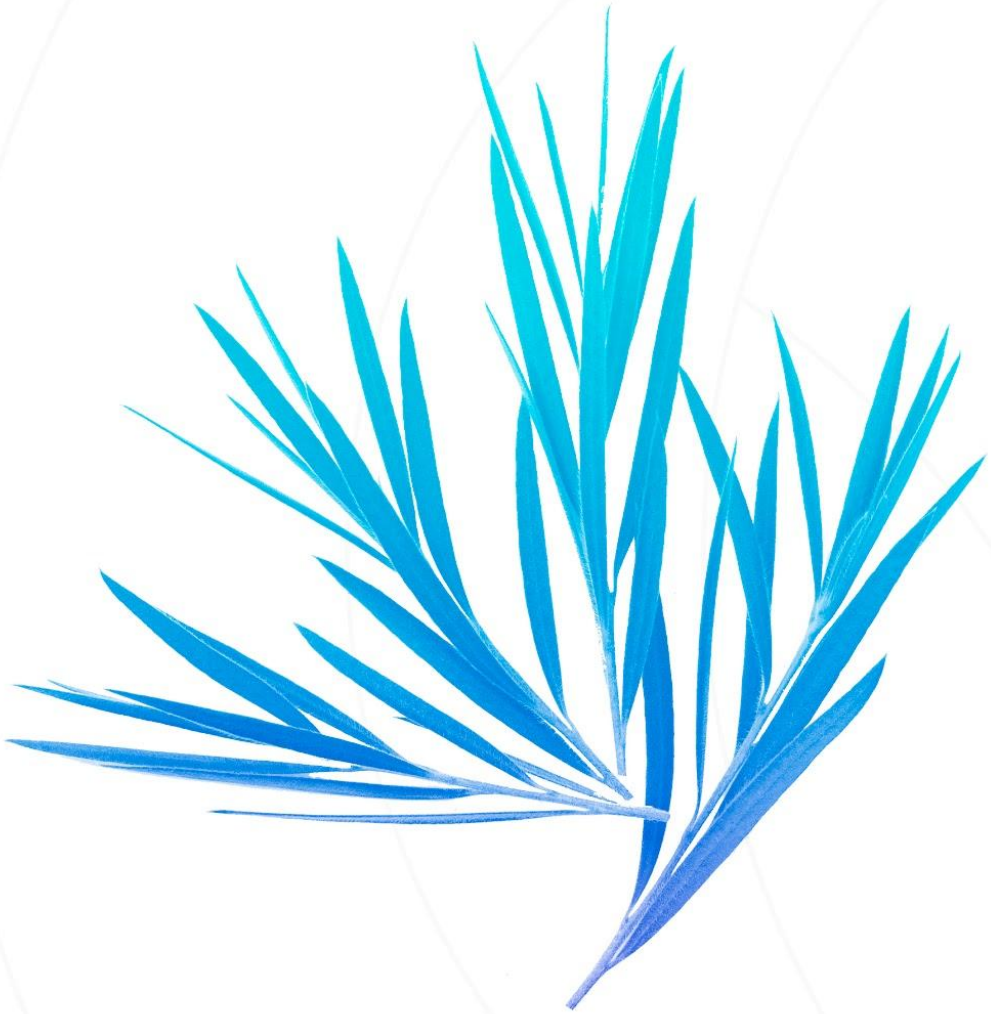
***Aflatoxins, fumonisins, and deoxynivalenol may induce environmental enteropathy, a mild malabsorption syndrome that manifests with villous atrophy, crypt hyperplasia, and T-cell infiltration.

PMID: 30447610/PMID: 33063532/PMID: 27417439

MYCOTOXINS: MECHANISMS OF DAMAGE

- Induce oxidative stress
- Deplete glutathione
- Disrupt the functions of enteric neurons
- Disrupt the intestinal epithelial barrier (aflatoxin B1/ochratoxin), cause intestinal cell death (zearalenone), impair gutr barrier leading to inflammation (food allergies, IBD), and possible enteropathy (malabsorption with villous atrophy)
- Influence the gut microbiota by altering its metabolic pathways: biosynthesis of short-chain fatty acids
- Including: the highly disrupted metabolic pathways for protein biosynthesis, pantothenate and acetyl CoA biosynthesis, betaine, cysteine, and methionine metabolism

PMID: 30447610/PMID: 33063532/PMID: 27417439/PMID: 29475160



THE GUT IS CONNECTED TO THE LIVER

REALITIES OF THE GUT-LIVER AXIS

TERMINOLOGY

- PAMPS – Pathogen-associated molecular patterns
- DAMPS – Cell damage associated molecular patterns
- LPS – Lipopolysaccharides: cell walls of gram negative bacteria
- Endotoxemia – The leakage of LPS through the gut lining and into the circulation

GUT-LIVER AXIS: A TWO-WAY STREET

Through portal vein:

- Short-chain fatty acids, secondary bile acids and 10% bilirubin is reabsorbed
- Ethanol, acetaldehyde, cytolysin, candidalysin, bacterial molecules, and exosomes can travel through the portal vein to the liver
- IF alcohol, pesticides, mycotoxins, persistent organic pollutants, and other toxicants are present – the tight junction barrier in gut can be breached and LPS (endotoxins) from gram-negative bacteria can be absorbed through portal vein
- LPS levels in blood are higher in Coronary Artery Disease, NAFLD, Obesity, DMII, Neuroinflammation, Neurodegeneration (AD and Parkinson's)

PMID: 33063532/33505393

METABOLIC ENDOTOXEMIA AS A RISK FACTOR FOR OBESITY, INSULIN RESISTANCE, & INFLAMMATION

- Endotoxemia risk is two-fold higher in the BMI-, sex-, and age-matched type 2 diabetes group than in the non-diabetic subjects.
- Fasting insulin significantly correlated with metabolic endotoxemia in the non-diabetic population when controlled for sex, age, and BMI.
- Obesity correlates with zonulin levels (elevated with high LPS).
- Positive association with endotoxemia and higher waist circumference (p = 0.003), diastolic blood pressure (p = 0.003), and glucose levels (p = 0.036) increased risk of overweight (p < 0.001), obesity (p = 0.047), hyperlipidemia (p = 0.048).
- Endotoxemia correlates with higher leptin/adiponectin ratio.
- Endotoxemia increases adipose levels of TNF-α and IL-6 concentrations and insulin resistance in healthy volunteers.

PMID: 30422702, 28282855

METABOLIC ENDOTOXEMIA AS A RISK FACTOR FOR NASH

- Endotoxin levels significantly higher in patients with NAFLD compared with controls NAFLD alone produced comparable endotoxin levels to T2DM.

- LPS binding protein was increased in patients with NASH (15.3±4.6 vs 13.8 ±3.3 μg/mL; P=.005) and F2-4 fibrosis (15.4±4.4 vs 14.0±3.7 μg/mL; P=.008) and significant fibrosis.

PMID: 26202818/20353583/28464257

SOLUTIONS

STRATEGIES TO SAVE THE GUT AND THEREFORE ALL OTHER ORGAN SYSTEMS

Biocidin Botanicals™

SOLUTIONS

PLOS ONE

RESEARCH ARTICLE

A cluster-randomized crossover trial of organic diet impact on biomarkers of exposure to pesticides and biomarkers of oxidative stress/inflammation in primary school children

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https://doi.org/10.1371/ journal.pone.0219420

ORGANIC VS. CONVENTIONAL FOODS IN 10–12 YEAR OLDS

- 149 children, 80-day randomized cross-over trial (40 days on organic & 40 days on conventional)
- Urinary pyrethroid and neonicotinoid pesticide metabolites were measured in both groups throughout the trial – six urine samples total
- Biomarkers of oxidative stress, inflammation: 8-iso-prostaglandin F2a [8-iso-PGF2a], malondialdehyde [MDA], and 8-hydroxy-2-deoxyguanosine [8-OHdG]); six urine samples at same time as pesticide samples

RESULTS:

The organic diet intervention reduced children's exposure to pyrethroid and neonicotinoid pesticides significantly. 23.4% of organic group had detectable pesticides at end of 40 days vs. 37.5% at the baseline.

At end of the 40-day organic period, lowered biomarkers of oxidative stress/inflammation:

- 8-OHdG (-1.7%)
- 8-iso-PGF2a (-1.6%)
- MDA (-0.1%)

THE NEW "DIRTY THIRTY" TO AVOID

- Non-organic soy, corn (that means NO Impossible Burgers)
- Non-organic grains/beans dessicated with glyphosate: oats, barley, wheat, beans, canola
- ESPECIALLY non-organic vegetables treated with the most toxic OP pesticides: broccoli, cauliflower, wheat, non-GMO corn
- Imported fruit/vegetables that are at high risk for toxic pesticide residue: orange, cucumber, apple, melon, banana
- Food high in PCBs: butter (either organic or nonorganic), farmed salmon, fatty meat, high-fat dairy (the Ketogenic Diet is still doable)
- What's left? USDA-certified organically grown food or locally grown food from growers you can trust.

Global Health 2012; 8:2 PMC3297498
Environ Health Perspect 2003;111:377–382

SOLUTIONS – PREBIOTICS & PROBIOTICS

- Co-treatment with inulin has been shown to prevent dysbiosis as well as early markers of dysmetabolism in rats chronically exposed to chlorpyrifos.

- In animal studies as well as human microbiome genomics studies, the number of *Bifidobacteria* is inversely correlated with body fat, glucose intolerance, and LPS level.

- Oligosaccharides like inulin-type fructans and galactooligosaccharides (GOS) are well supported for their prebiotic effects on microbial composition, mainly due to the increased proportions of *Bifidobacterium* and *Lactobacillus.*

- **Examples of prebiotics:** fructooligosaccharides, gluco-oligosaccharides, isomaltooligosaccharides, maltooligosaccharides, lactulose, soy raffinose oligosaccharides, stachyose, xylo-oligosaccharides, resistant starch (green banana flour), and inulin-resistant starch.

PMID: 33837455
PMID: 30581114

High Fiber Diet vs Fermented Foods Study

Published in final edited form as:
Cell. 2021 August 05; 184(16): 4137–4153.e14. doi:10.1016/j.cell.2021.06.019.

Gut Microbiota-Targeted Diets Modulate Human Immune Status

Hannah C. Wastyk[#2], Gabriela K Fragiadakis[#1], Dalia Perelman[3], Dylan Dahan[1], Bryan D Merrill[1], Feiqiao B. Yu[5], Madeline Topf[1], Carlos G. Gonzalez[4], William Van Treuren[1], Shuo Han[1], Jennifer L. Robinson[3], Joshua E. Elias[4], Erica D. Sonnenburg[1,6,†], Christopher D. Gardner[3,†], Justin L. Sonnenburg[1,6,†,≠]

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"The high-fiber diet increased microbiome-encoded glycan-degrading CAZymes despite stable microbial community diversity.

While Cytokine Response Score (primary outcome) was unchanged, three distinct immunological trajectories in high fiber-consumers corresponded to baseline microbiota diversity.

Alternatively, the high-fermented food diet steadily increased microbiota diversity and decreased inflammatory markers. Fermented foods may be valuable in countering the decreased microbiome diversity and increased inflammation pervasive in industrialized society."

doi:10.1016/j.cell.2021.06.019.

SPORE-BASED PROBIOTICS

- Study: **"Oral spore-based probiotic supplementation was associated with reduced incidence of postprandial dietary endotoxin, triglycerides, and disease risk biomarkers."**
- 75 individuals with postprandial endotoxemia
- Half were given *Bacillus indicus* (HU36), *Bacillus subtilis* (HU58), *Bacillus coagulans*, *Bacillus licheniformis*, and B*acillus clausii* x 30 days. Endotoxin assay was repeated 30 days later.
- **Spore-based probiotic supplementation** was associated with a **42% reduction** in endotoxin (12.9 ± 3.5 vs 6.1 ± 2.6, P = 0.011) and a **24% reduction** in triglyceride (212 ± 28 vs 138 ± 12, P = 0.004) in the postprandial period.
- Placebo subjects presented with a 36% increase in endotoxin (10.3 ± 3.4 vs 15.4 ± 4.1, P = 0.011) and a 5% decrease in triglycerides (191 ± 24 vs 186 ± 28, P = 0.004) over the same postprandial period.
- Compared to placebo, probiotic subject had less ghrelin (6.8 ± 0.4 vs 8.3 ± 1.1, P = 0.017).

PMID: 28868181

TREATMENT: ORGANOPHOSPHATE PESTICIDE EXPOSURE

- N-acetyl cysteine (NAC) – animal studies
- Curcumin alone: dosage equivalent 2,500 mg (50 mg/kg)
- Curcumin with NAC – prevents DNA damage and lipid peroxidation dosage: 1,800 mg NAC
- Melatonin – with vitamins C and E prevents DNA damage and lipid peroxidation associated with chlorpyrifos; dosage equivalent: melatonin 3 mg hs
- Melatonin – used in treatment of acute OP poisoning in India, up to 20 mg

J Biochem Mol Toxicol. 2010 Sep-Oct;24(5):286-92./ *Arch Toxicol* 2001;75(2):88–96.
Biol Pharm Bull. 2007 Mar;30(3):490-4
Cell Biol Toxicol. 2008 Apr;24(2):151-8.
Toxicol Ind Health 2012 DOI: 10.1177/0748233712446726

PON1 RISK ALLELE:
THE CANARY OF PESTICIDE TOXICITY

- PON1 – paraoxonase 1 determines the rate at which organophosphate pesticides are metabolized.
- Those with the "slower" PON1 snps: PON1-$_{192QQ}$ and PON1$_{55MM}$ who reported using OP pesticides at their homes had an increased risk of Parkinson's Disease of 2.84/3.57, respectively.
- "Genetic susceptibility alone does not increase the risk of PD in the absence of exposure to OP pesticides."

PMID: 23602893

UPREGULATE PON1 ACTIVITY

Increased activity of PON1 even with PON1 snps:

- Exercise
- Mediterranean diet
- Olive oil
- Fish oil
- Pomegranate
- Anthocyanins (berries)
- Coconut oil
- Quercetin
- Walnuts
- Aspirin

PMID: 23710701, 25963585, 26761772, 16276071, 22924372, 23510814, 24285687, 25758596, 20228421, 17585031, 23892389, 19891963

TREATMENT: PRESERVE GLUTATHIONE STATUS

Decrease oxidative stress:

- Alpha lipoic acid has been shown to increase glutathione levels and upregulate ATP production acting as an antioxidant in mitochondria. When rats are pre-treated with ALA (20 mg/kg) and then exposed to malathion they did not have liver or kidney degenerative changes that occurred without the ALA.
- Vit. D – sufficient to raise blood levels to 50-80 ng/ml: for every 1,000 IU vit. D you supplement blood levels go up: 10 ng/ml or 25 nmol/L

Neurochem Res 2008;33:194-203.
Am J. Clin Nutr 2003;77:204-210.
Trends Endocrinol Metab. 2002 Apr;13(3):100-5.
Am J Kidney Dis. 2001 Apr;37(4):750-7.
J Biomed Biotechnol. 2010; 2010: 203503.

LOE: C

DHA (OMEGA-3 DOCOSAHEXAENOIC ACID)

- DHA crosses the blood-brain barrier, protecting cell membranes from toxin-induced oxidative damage, particularly from organophosphate and carbamate pesticides.
- DHA from marine algae or fish/krill oil: 750 mg daily

Neurochem Int. 2011; 59:664–70. LOE: B

ASCORBATE: AN ESSENTIAL NUTRIENT TO SURVIVE IN 2023

- Buffered ascorbate (calcium, magnesium, potassium, zinc) also alkalinizes urine leading to improved renal excretion of toxicants.
- Functions as an electron donor to enhance cell energy. Ascorbate is uniquely able to donate an electron and restore ATP-generating capacity to the mitochondria of the cell, thus increasing its energy output.
- Functions as an antioxidant to reduce and support glutathione.
- Individual needs vary, minimum dose 3,000 mg. Tolerance test may show need for greater doses.

Int J Vitam Nutr Res.2009 Sep; 79(5-6):281-7. Intl J Integrative Med, 2000; 2(6):7-18.
Annu Rev Nutr. 1986; 6:365-406

VITAMIN E COMPLEX

- Vitamin E (1000 IU) – helps stabilize cell membranes while quenching free radical damage.
- Organophosphates and carbamates cause extensive oxidative damage, especially to the cardiovascular and nervous systems. Data indicate vitamin E prevents damage in organophosphate exposure.

J Neurochem 2007;100(6):1469./Oxid Med Cell Longevity 2014 Article ID 671539.

VITAMIN A / CAROTENOIDS

- 50,000 IU daily
- Organophosphates and PCBs decrease liver Vit. A content, which increases their toxicity.
- IM injection of 1,500,000 units Vit A given yearly to cattle to treat organophosphate poisoning.
- Other items that lower Vit. A stores: alcohol, coffee, cold weather, cortisone, diabetes, excessive Fe, infections, laxatives, liver disease, mineral oil, nitrates, sugar, tobacco, Vit. D deficiency, Zn deficiency.
- Carotenoids have no Vit. A-related toxicity, as the conversion to Vit. A is rate-limited in intestinal lining. Conversion is limited in diabetics and documented increased risk for lung CA in smokers.

Mar. Drugs 2015, *13*, 6152-6209.

POLYPHENOLS TO THE RESCUE

- Apocynin (*Picrorhiza kurroa)* – in animal studies prevents the gut permeability and zonulin expression resulting from oral PCB exposure.
- Quercetin – inhibits hepatotoxicity and endothelial inflammation from PCB exposure.
- EGCG (green tea extract) – epigenetic effect on inflammation: IL-6, IL- 1, C-reactive protein, intercellular adhesion molecule-1 (ICAM- 1), and VCAM-1.
- Caffeic acid derivatives – chlorogenic acid (coffee), ferulic acid (barley, oats, bamboo shoots), and rosmarinic acid (Rosemary) inhibit hepatotoxicity of PCBs.
- Genistein (soy isoflavone) – protects against inflammation in human macrophage culture (interferon g, IL-1RA, IL-8, IL-10, and MIB-1b).
- Resveratrol/EGCG – prevents endothelial inflammation (oxidant stress).
- Curcumin – evidence for prevention of insulin resistance caused by BPA due to pancreatic beta-cell damage.

doi:10.1289/ehp.0901751/doi:10.1016/j.envpol.2018.07.039
PMID: 31563713