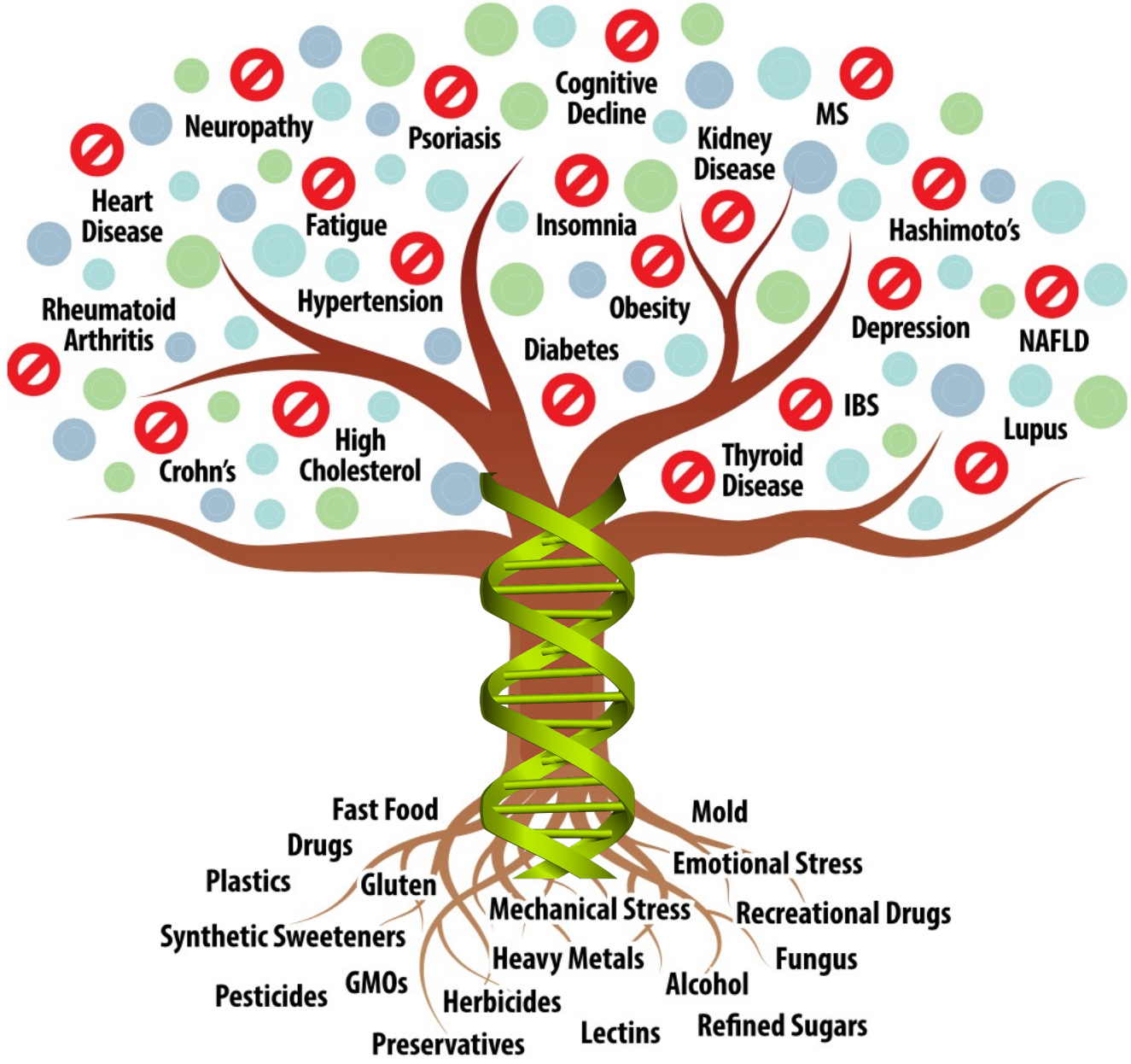
Clinical Manifestations on Gut-Brain Connections

A Biogenetix Clinical Presentation

BIOGENETIX.COM

Disclaimer

- *Information in this presentation is not intended, in itself, to diagnose, treat, reverse, cure, or prevent any disease. While this presentation is based on medical literature, findings, and text, The following statements have not been evaluated by the FDA.*
- *The information provided in this presentation is for your consideration only as a practicing health care provider. Ultimately you are responsible for exercising professional judgment in the care of your own patients.*


Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Herbicides
Alcohol
Lectins
Refined Sugars
Preservatives

Front Neurol. 2019; 10: 883.
Published online 2019 Aug 13. doi: 10.3389/fneur.2019.00883
PMCID: PMC6700295
PMID: 31456743

Crosstalk Between the Gut Microbiota and the Brain: An Update on Neuroimaging Findings

Ping Liu,[1,†] Guoping Peng,[1,†] Ning Zhang,[2] Baohong Wang,[3] and Benyan Luo[1,*]

An increasing amount of evidence suggests that bidirectional communication between the gut microbiome and the central nervous system (CNS), which is also known as the microbiota-gut-brain axis, plays a key role in the development and function of the brain. For example, alterations or perturbations of the gut microbiota (GM) are associated with neurodevelopmental, neurodegenerative, and psychiatric disorders and modulation of the microbiota-gut-brain axis by probiotics, pre-biotics, and/or diet induces preventative and therapeutic effects. The current interpretation of the mechanisms underlying this relationship are mainly based on, but not limited to, parallel CNS, endocrine, and immune-related molecular pathways that interact with each other. Although many studies have revealed the peripheral aspects of this axis, there is a paucity of data on how structural and functional changes in the brain correspond with gut microbiotic states *in vivo*. However, modern neuroimaging techniques and other imaging modalities have been increasingly applied to study the structure, function, and molecular aspects of brain activity in living healthy human and patient populations, which has resulted in an increased understanding of the microbiota-gut-brain axis. The present review focuses on recent studies of healthy individuals and patients with diverse neurological disorders that employed a combination of advanced neuroimaging techniques and gut microbiome analyses. First, the technical information of these imaging modalities will be briefly described and then the included studies will provide primary evidence showing that the human GM profile is significantly associated with brain microstructure, intrinsic activities, and functional connectivity (FC) as well as cognitive function and mood.

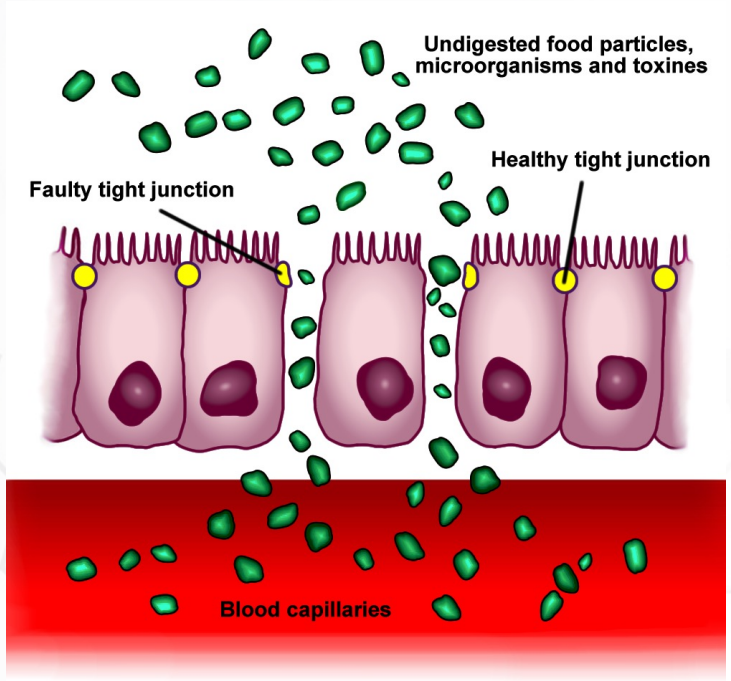
Front Neurol. 2019; 10: 883.
Published online 2019 Aug 13. doi: 10.3389/fneur.2019.00883
PMCID: PMC6700295
PMID: 31456743

Crosstalk Between the Gut Microbiota and the Brain: An Update on Neuroimaging Findings

Ping Liu,[1,†] Guoping Peng,[1,†] Ning Zhang,[2] Baohong Wang,[3] and Benyan Luo[1,*]

Author information ▸ Article notes ▸ Copyright and License information ▸ Disclaimer

Regarding neurological disorders, hepatic encephalopathy (HE) presents as a spectrum of neuropsychiatric symptoms that range from subtle fluctuations in cognition to coma (64). Alterations in the GM as well as related metabolomes, such as amino acid metabolites and endotoxins, could lead to the occurrence of HE when occurring against a background of intestinal hyperpermeability (i.e., leaky gut) and systemic inflammation. Using a combination of cognitive testing, assessments of stool microbiota, brain MRI analyses, and evaluations of systemic inflammation, Ahluwalia et al. (28) identified a robust correlation network in which autochthonous bacterial families (*Lachospiraceae, Ruminococcaeae*, and *Clostridiales XIV*) are negatively correlated with liver function and glial MRS manifestations of ammonia (high Glx levels with low mi and Cho levels) in the brain, especially in subjects with HE. The same research group assessed elderly outpatients with or without cirrhosis and found that elderly patients had an altered gut-brain axis regardless of the presence of cirrhosis, which suggests that cognitive function is influenced by alterations in the GM *per se*. In another study, MRS was used to evaluate the metabolic and neurobiological substrates of the brain, and the amnestic/non-amnestic group had a decreased mi/Cr ratio and a reduced NAA-NAAG/Cr ratio in the anterior cingulate cortex. The cognitively impaired groups had a significantly lower relative abundance of genera belonging to autochthonous and beneficial taxa (27).



INFLAMMATORY, IMMUNOLOGICAL,
AUTOIMMUNE AND NEOPLASTIC REACTIONS

Gastroenterol Rep (Oxf). 2017 May; 5(2): 138–147.
Published online 2017 Apr 18. doi: 10.1093/gastro/gox013
PMCID: PMC5421503
PMID: 28533911

Hepatic encephalopathy

Peter Ferenci

Hepatic encephalopathy (HE) is a reversible syndrome of impaired brain function occurring in patients with advanced liver diseases. The precise pathophysiology of HE is still under discussion; the leading hypothesis focus on the role of neurotoxins, impaired neurotransmission due to metabolic changes in liver failure, changes in brain energy metabolism, systemic inflammatory response and alterations of the blood brain barrier. HE produces a wide spectrum of nonspecific neurological and psychiatric manifestations. Minimal HE is diagnosed by abnormal psychometric tests. Clinically overt HE includes personality changes, alterations in consciousness progressive disorientation in time and space, somnolence, stupor and, finally, coma. Except for clinical studies, no specific tests are required for diagnosis. HE is classified according to the underlying disease, the severity of manifestations, its time course and the existence of precipitating factors. Treatment of overt HE includes supportive therapies, treatment of precipitating factors, lactulose and/or rifaximin. Routine treatment for minimal HE is only recommended for selected patients.

Review > Food Funct. 2018 Mar 1;9(3):1373-1388. doi: 10.1039/c7fo01528c.
Epub 2018 Feb 27.

Gut : liver : brain axis: the microbial challenge in the hepatic encephalopathy

Andrea Mancini [1] Francesca Campagna [2] Piero Amodio [2] Kieran M Tuoby [1]

Hepatic encephalopathy (HE) is a debilitating neuropsychiatric condition often associated with acute liver failure or cirrhosis. Advanced liver diseases are characterized by a leaky gut and systemic inflammation. There is strong evidence that the pathogenesis of HE is linked to a dysbiotic gut microbiota and to harmful microbial by-products, such as ammonia, indoles, oxindoles and endotoxins. Increased concentrations of these toxic metabolites together with the inability of the diseased liver to clear such products is thought to play an important patho-ethiological role. Current first line clinical treatments target microbiota dysbiosis by decreasing the counts of pathogenic bacteria, blood endotoxemia and ammonia levels. This review will focus on the role of the gut microbiota and its metabolism in HE and advanced cirrhosis. It will critically assess data from different clinical trials measuring the efficacy of the prebiotic lactulose, the probiotic VSL#3 and the antibiotic rifaximin in treating HE and advanced cirrhosis, through gut microbiota modulation. Additionally data from Randomised Controlled Trials using pre-, pro- and synbiotic will be also considered by reporting meta-analysis studies. The large amount of existing data showed that HE is a clear example of how an altered gut microbiota homeostasis can influence and impact on physiological functions outside the intestine, with implication for host health at the systems level. Nevertheless, a strong effort should be made to increase the information on gut microbiota ecology and its metabolic function in liver diseases and HE.

Toxins Summary			
		Current	Previous Result
Environmental Toxins	Organochlorine pesticides		
	Organophosphate pesticides		
	Other pesticides/herbcides	Glyphosate 🔴	
	Phthalate Metabolites		
	Parabens	Methylparaben 🔴	
	Acrylic Metabolites		
	Other Metabolites	N-Acetyl Propyl Cysteine (NAPR) 🟡, Diphenyl Phosphate (DPP) 🔴	
	Alkylphenol	Bisphenol A (BPA) 🟡	
	Volatile Organic Compounds (VOCs)	3-Methylhippuric Acid (3MHA) 🔴, 4-Methylhippuric Acid (4MHA) 🔴	
	Urine Creatinine		
Mycotoxins V2	Aflatoxin	Aflatoxin M1 🔴	
	Other	Ochratoxin A 🔴, Fumonisins B1 🟡, Chaetoglobosin A 🟡	
	Trichothecenes	diacetoxyscirpenol (DAS) 🔴	
	Urinary Creatinine		
Heavy Metals	Heavy Metals (Creatinine)		

Mycotoxins - High

Test Name	Species Name	In Control	Moderate	High	Current Level	Previous Level
Aflatoxin M1 (ng/g)	Aspergillus	≤4.80	4.81~9.60	≥9.61	19.51	
Ochratoxin A (ng/g)	Aspergillus, Penicillium	≤5.10	5.11~10.20	≥10.21	18.01	
diacetoxyscirpenol (DAS) (ng/g)	Fusarium	≤3.20	3.21~6.40	≥6.41	18.18	

Mycotoxins - Moderate

Test Name	Species Name	In Control	Moderate	High	Current Level	Previous Level
Fumonisins B1 (ng/g)	Fusarium	≤4.60	4.61~9.20	≥9.21	7.09	
Chaetoglobosin A (ng/g)	Chaetomium globosum	≤23.90	23.91~47.80	≥47.81	39.29	

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▲	**Glucose** [01]	**188**	**High**		mg/dL	65-99
	BUN [01]	16			mg/dL	6-24
	Creatinine [01]	0.90			mg/dL	0.76-1.27
	eGFR	98			mL/min/1.73	>59
	BUN/Creatinine Ratio	18				9-20
	Sodium [01]	137			mmol/L	134-144
	Potassium [01]	4.3			mmol/L	3.5-5.2
	Chloride [01]	99			mmol/L	96-106
▼	**Carbon Dioxide, Total** [01]	**19**	**Low**		mmol/L	20-29
	Calcium [01]	10.0			mg/dL	8.7-10.2
	Protein, Total [01]	7.9			g/dL	6.0-8.5
▲	**Albumin** [01]	**5.5**	**High**		g/dL	3.8-4.9
	Globulin, Total	2.4			g/dL	1.5-4.5
▲	**A/G Ratio**	**2.3**	**High**			1.2-2.2
	Bilirubin, Total [01]	0.4			mg/dL	0.0-1.2
▼	**Alkaline Phosphatase** [01]	**35**	**Low**		IU/L	44-121
	AST (SGOT) [01]	36			IU/L	0-40
	ALT (SGPT) [01]	37			IU/L	0-44

Hgb A1c with eAG Estimation

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
▲	**Hemoglobin A1c** [01]	**9.0**	**High**		%	4.8-5.6
	Please Note: [01]	Prediabetes: 5.7 - 6.4 Diabetes: >6.4 Glycemic control for adults with diabetes: <7.0				
	Estim. Avg Glu (eAG)	212			mg/dL	

	Test	Current Result and Flag		Previous Result and Date	Units	Reference Interval
	Lipids [01]					
▲	**Cholesterol, Total** [01]	**278**	**High**		mg/dL	100-199
▲	**Triglycerides** [01]	**336**	**High**		mg/dL	0-149
	HDL Cholesterol [01]	43			mg/dL	>39
▲	**VLDL Cholesterol Cal**	**65**	**High**		mg/dL	5-40
▲	**LDL Chol Calc (NIH)**	**170**	**High**		mg/dL	0-99
▲	**T. Chol/HDL Ratio**	**6.5**	**High**		ratio	0.0-5.0

Front Cell Infect Microbiol. 2018; 8: 60.
Published online 2018 Feb 26. doi: 10.3389/fcimb.2018.00060
PMCID: PMC5834427
PMID: 29535978

Mycotoxin: Its Impact on Gut Health and Microbiota

Winnie-Pui-Pui Liew and Sabran Mohd-Redzwan*

Author information Article notes Copyright and License information Disclaimer

Trichothecenes *Fusarium graminearum* is the main fungi species that produces tricothecenes. All tricothecenes contain an epoxide at the C12, C13 positions, which is responsible for their toxicological activity (Nathanail et al., 2015). T-2 toxin (Type A) and DON (Type B) are the major mycotoxins that cause toxicity to humans and animals via oral ingestion (Nathanail et al., 2015).

During World War II, a biological weapon caused an acute syndrome consists of cough, sore throat, dyspnea, bloody nasal discharge, and fever was reported by Soviet scientists (Pitt and Miller, 2016). Twenty years later, T-2 mycotoxin was discovered when civilians consumed wheat that was unintentionally contaminated with Fusarium fungi (Pitt and Miller, 2016). A human toxicosis due to ingestion of moldy rice contaminated with T-2 toxin has been reported in China. According to Wang Z. et al. (1993), 65% of patients developed food poisoning symptoms such as chills, nausea, abdominal distension, dizziness, vomiting, thoracic stuffiness, abdominal pain, and diarrhea. Similar to T-2 toxicity, victims of DON outbreak suffered from vomiting syndromes (Etzel, 2014). Several outbreaks of acute DON toxicity in human have been reported in India, China, and the USA (Etzel, 2014).

Front Cell Infect Microbiol. 2018; 8: 60.
Published online 2018 Feb 26. doi: 10.3389/fcimb.2018.00060
PMCID: PMC5834427
PMID: 29535978

Mycotoxin: Its Impact on Gut Health and Microbiota

Trichothecenes toxic effects in animals (dairy cattle, swines, broilers, and rats) include decreased plasma glucose, reduced blood cell and leukocyte count, weight loss, alimentary toxic aleukia, as well as pathological changes in the liver and stomach (Adhikari et al., 2017). The mechanism involved in T-2 and DON toxicity is generally via oxidative stress-mediated deoxyribonucleic acid (DNA) damage and apoptosis (Wu et al., 2014). Furthermore, T-2 and DON are well-known inhibitors of protein synthesis resulting from the binding of peptidyl-transferase, which is located in the 60s ribosomal subunit (Yang et al., 2017).

In the GI tract, a decreased absorption of glucose was observed following T-2 and DON intoxication resulted from suppressed SGLT1 (glucose transporter) mRNA expression. Apart from the glucose absorption, SGLT1 also responsible for water reabsorption, thus reduction of SGLT1 transporter induces diarrhea as well (Grenier and Applegate, 2013).

The weight loss effect of trichothecenes involved neuroendocrine factors and cytokines. DON and T-2 elevated concentrations of the indoleamines, serotonin and 5-hydroxy-3-indoleacetic acid (HIAA) in all brain regions (Wang J. et al., 1993). These neuroendocrine factors can affect the secretion of both anorexigenic and/or orexigenic hormones (Maresca, 2013). Through increasing gene expression of anorexia-inducing proinflammatory cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), trichothecenes exacerbate the condition of anorexia (Wu et al., 2015). In addition, DON and T-2 also induced the release of the satiety hormones, peptide YY (PYY) and cholecystokinin (CCK), which are critical mediators of anorexia (Wu et al., 2015).

Front Cell Infect Microbiol. 2018; 8: 60.
Published online 2018 Feb 26. doi: 10.3389/fcimb.2018.00060
PMCID: PMC5834427
PMID: 29535978

Mycotoxin: Its Impact on Gut Health and Microbiota

Winnie-Pui-Pui Liew and Sabran Mohd-Redzwan*

Using animal models, trichothecenes was found to induce necrotic lesions in the GI tract (Kolf-Clauw et al., 2013). A shortening of villi height was also observed in trichothecenes-treated animals (swine, poultry, and rat model). The changes on villi were due to activation of the apoptotic pathway by trichothecenes, which in turn leads to nutrition malabsorption (Alizadeh et al., 2015). Furthermore, results obtained from *in vivo* and *in vitro* studies showed that trichothecenes increased intestinal permeability. Using porcine epithelial cell, trichothecenes increased the intestinal permeability by lowering tight junction proteins expression (Osselaere et al., 2013). In addition, previous studies revealed a significant ($P < 0.05$) decreased in the number of goblet cells that secrete mucin in trichothecenes-treated animals. Mucin is primarily involved in the gut barrier function (Pinton and Oswald, 2014). The disruption in the integrity of intestinal epithelium allows the entry of the pathogen into the gut lumen (Lessard et al., 2015). Besides, trichothecenes have been linked with a decreased level of IL-8 in the intestine, which is responsible for pathogen removal (Kadota et al., 2013). Overall, trichothecenes exert negative impacts on GI tracts specifically on the gut absorption, integrity, and immunity.


CRISPs
CRISPs
SUPERBITES
SUPERBITES
ONION RINGS
partymix

Table 1 https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7830705/

Studies on the occurrence of trichothecenes (TCT) distribution (µg/kg) in food and feed samples around the world during 2011–2020.

Food/Feed Matrix	Country	TCT	N Samples	% Positive Samples	Mean [µg/kg]	Range [µg/kg]	Detection Technique	Reference
Barley, maize, rice and wheat grains	Algeria	DON	120	33.3	588	48–2055	UHPLC-MS/MS	[70]
		HT-2		23	18.1	8.4–36.7		
		T-2		100	24.9	16.6–47.2		
Wheat	Poland	DON	92	83	140	10–1265	HPLC	[71]
Wheat	China	DON	181	82	500	33–3030	HPLC	[72]
Wheat	Brazil	DON	172	77	234	73–2794	HPLC	[73]
Wheat	Brazil	DON	48	100	2398	1329–3937	HPLC	[74]
Wheat	Brazil	DON	53	47	641	243–2281 1866	HPLC	[75]
Barley	Brazil	DON	76	94	310–15500	1700–7500	LC-MS/MS	[89]
Infant foods	India	DON	29	66	NA	5–228	ELISA	[90]
Corn flour	Serbia	DON	56	42.90	101	NA–931	HPLC	[91]
Pasta and noodles	Germany	DON	40	97	387	60–1609	HPLC	[76]

Toxins (Basel). 2019 Nov; 11(11): 634.
Published online 2019 Oct 31. doi: 10.3390/toxins11110634
PMCID: PMC6891312
PMID: 31683661

Trichothecenes in Cereal Grains – An Update

Nora A. Foroud,[1,*] Danica Baines,[1] Tatiana Y. Gagkaeva,[2] Nehal Thakor,[3] Ana Badea,[4] Barbara Steiner,[5]

Due to the significant health implications of trichothecene exposure in humans and animals, limits are placed on the allowance of trichothecenes in different food/feed products. North American and European guidelines for trichothecenes in human and animal food differ both in terms of the acceptable concentration limits and the specific affected commodities. These guidelines, summarized in Table 7 and Table 8, are provided by the Canadian Food Inspection Agency, the United States Food and Drug Administration, and the European Commission Regulations.

DON allowance in food and feed.

Food products	
Finished wheat products for consumption by humans	1000 ppb (USA)
Uncleaned soft wheat for human consumption	2000 ppb (Canada)
Unprocessed cereals (excluding durum wheat, oats, and maize)	1250 ppb (Europe)
Unprocessed durum wheat and oats	1750 ppb (Europe)
Unprocessed maize	1750 ppb (Europe)
Cereal flour, maize flour, maize, grits, and maize meal	750 ppb (Europe)
Bread, biscuits, pastries, cereal snacks and breakfast cereals	500 ppb (Europe)
Dry pasta	750 ppb (Europe)
Processed cereal based baby and infant food	200 ppb (Europe)

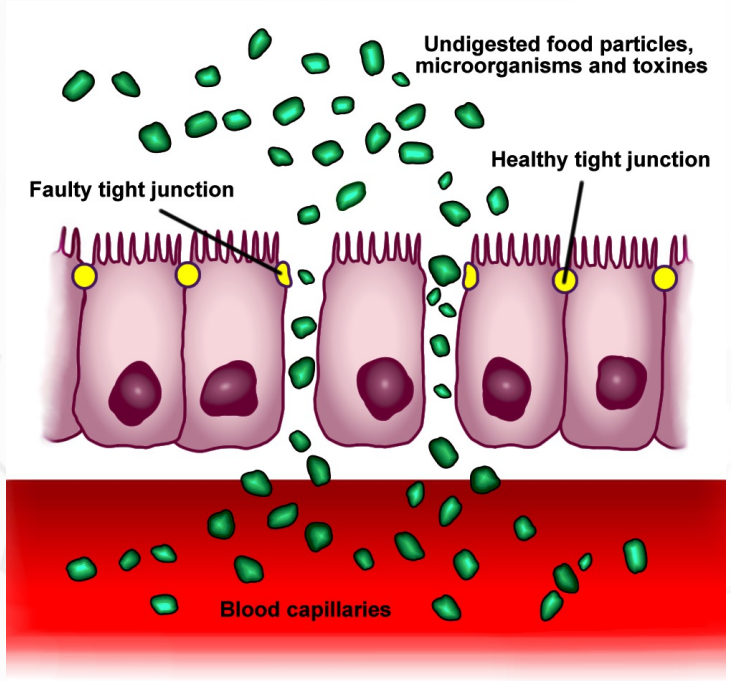
Toxins (Basel). 2019 Nov; 11(11): 634.
Published online 2019 Oct 31. doi: 10.3390/toxins11110634
PMCID: PMC6891312
PMID: 31683661

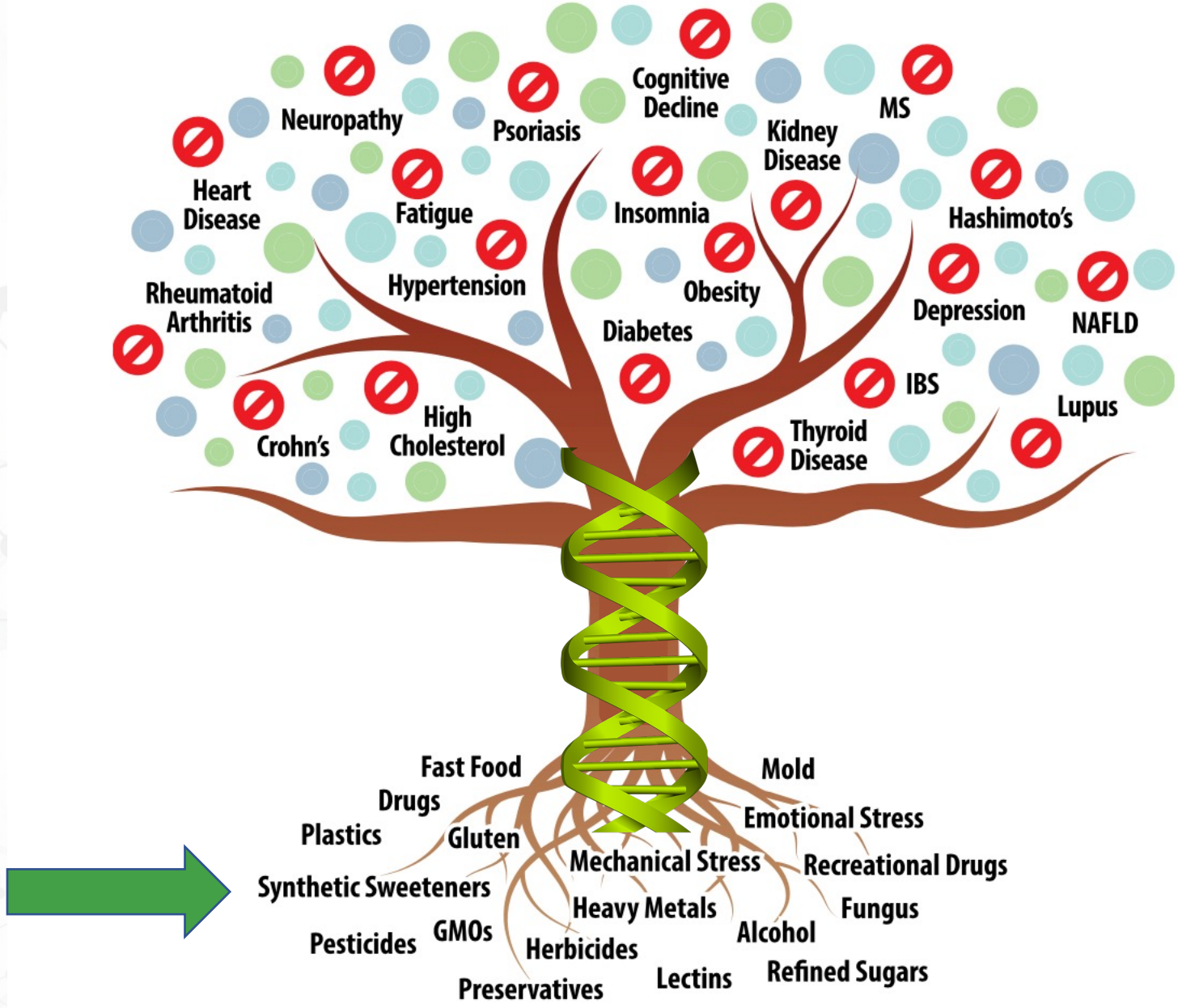
Trichothecenes in Cereal Grains – An Update

Nora A. Foroud,[1,*] Danica Baines,[1] Tatiana Y. Gagkaeva,[2] Nehal Thakor,[3] Ana Badea,[4] Barbara Steiner,[5]

Feed	
Grains and grain by-products destined for ruminating beef and feedlot cattle older than 4 months and for chickens	10 ppm (Europe)
Grains and grain by-products destined for ruminating beef and feedlot cattle older than 4 months and chickens (not exceeding 50% of the cattle or chicken total diet)	10 ppm (USA)
Grains and grain by-products destined for ruminating beef and feedlot cattle older than 4 months and chickens (not exceeding 50% of the cattle or chicken total diet)	5 ppm (Canada)
Grain and grain by-products destined for swine	5 ppm (Europe)
Grain and grain by-products destined for swine	5 ppm (USA)
Grain and grain by-products destined for swine	1 ppm (Canada)
Grain and grain by-products destined for other animals	5 ppm (Europe)

The *Fusarium* trichothecenes that contaminate cereal-based food and feed have had devastating impacts on human history. While our ability to monitor and limit their entry into the food/feed chain has improved over the years, they continue to persist, and this can have significant economic impacts as well health safety risks. The pathogens continue to evolve, and new emergent and masked mycotoxins are being identified [62,391]. In spite of the controls in place to regulate these toxins in food/feed, DON has been detected in the urine of different human populations [262], including children [264]. Thus, continued research efforts are needed to reduce trichothecene contamination of food and feed.




Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten
Mechanical Stress
Recreational Drugs
Synthetic Sweeteners
Heavy Metals
Fungus
Pesticides
GMOs
Herbicides
Alcohol
Lectins
Refined Sugars
Preservatives

Biogenetix: 833-525-0001

kim@biogenetix.com