A Unified Theory of Disease

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Disclosure

Joe Pizzorno, ND disclosed he was on the advisory board for Bioclinic Naturals and his spouse is a consultant for AlgaeCal.

Outline

- Humans are Complex, Synchronous Enzyme Machines
- Themes
  1. Nutrient Deficiencies Rampant
  2. High Body Load of Toxic Metals and Chemicals
  3. Deficiencies + Toxins Synergistically Increase Damage
  4. Human Physiology Massively Parallel—Few Single Pathways
  5. Modern Agriculture Dangerously Distorts Food Supply
  6. Organically-Grown Foods More Healthful than Chemically-Grown Foods
  7. Loss of Synchronization with the Environment
- Putting It All Together
- Take Home Message

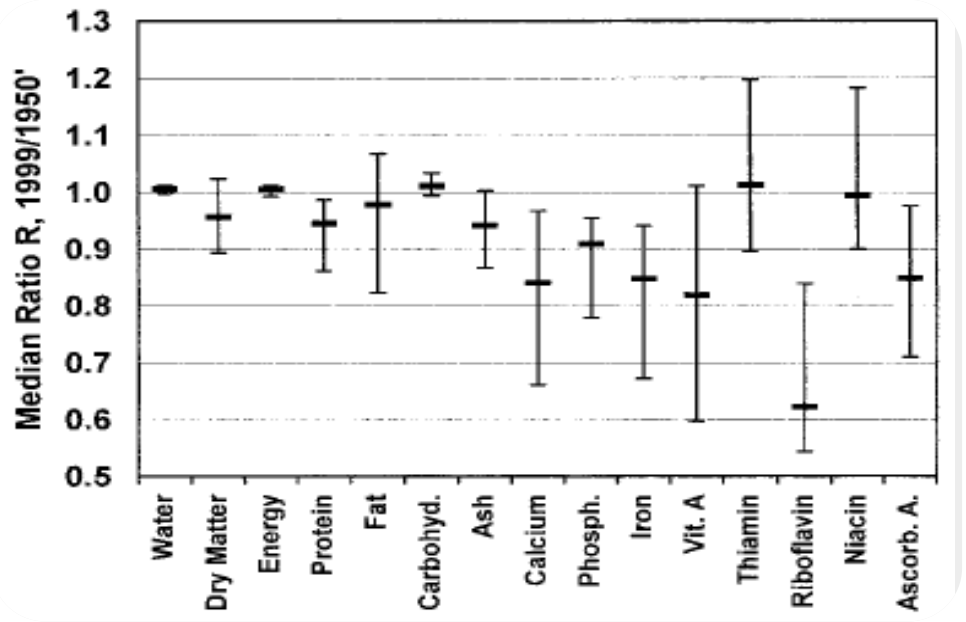
HUMANS ARE COMPLEX, SYNCHRONOUS ENZYME MACHINES

Theme 1

NUTRIENT DEFICIENCIES RAMPANT

Decreasing Nutrient Density (1950-1999)

- 43 foods (mainly vegetables)
- 13 nutrients measured
- 6 significantly low
  - Biggest drop 37% in riboflavin
- Did not measure trace minerals!



"Changes in seed types …not fertilizer."

Davis DR, et al. Changes in USDA Food Composition Data for 43 Garden Crops, 1950 to 1999. J Am Coll Nutr 2004; 23:669–82

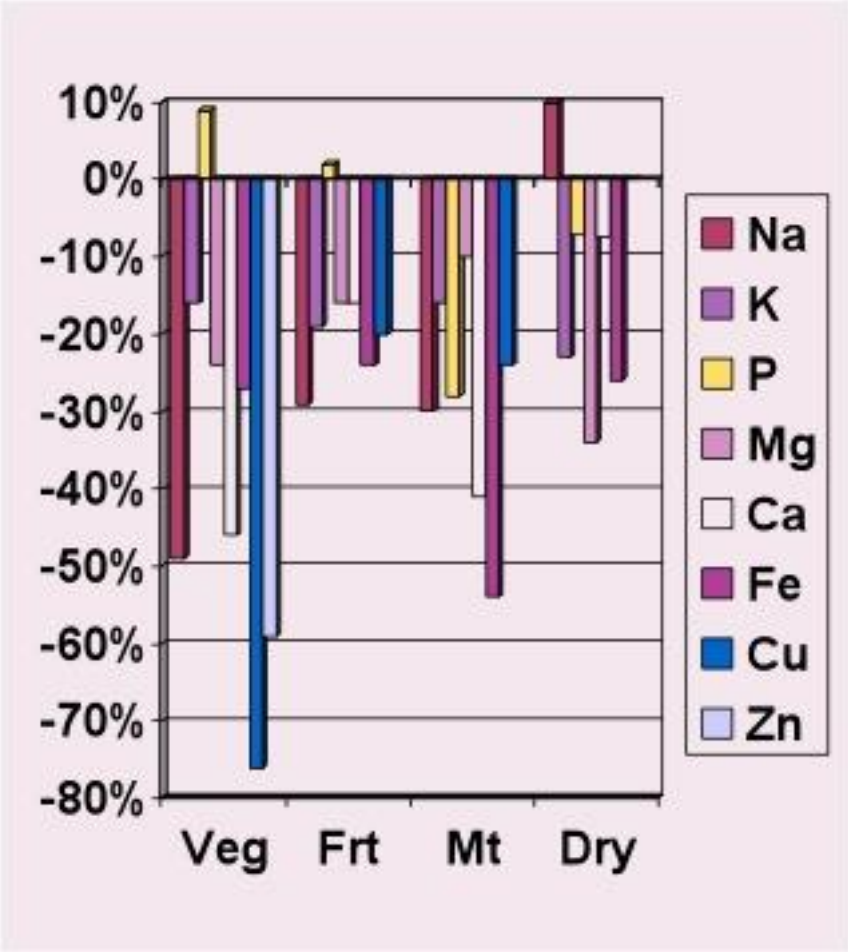
Chemical Fertilizers Decrease Minerals (1940-1991)

Commonly eaten foods

- Vegetables – 27
- Fruits – 17
- Meats – 10
- Dairy – 2
- Fish – no data

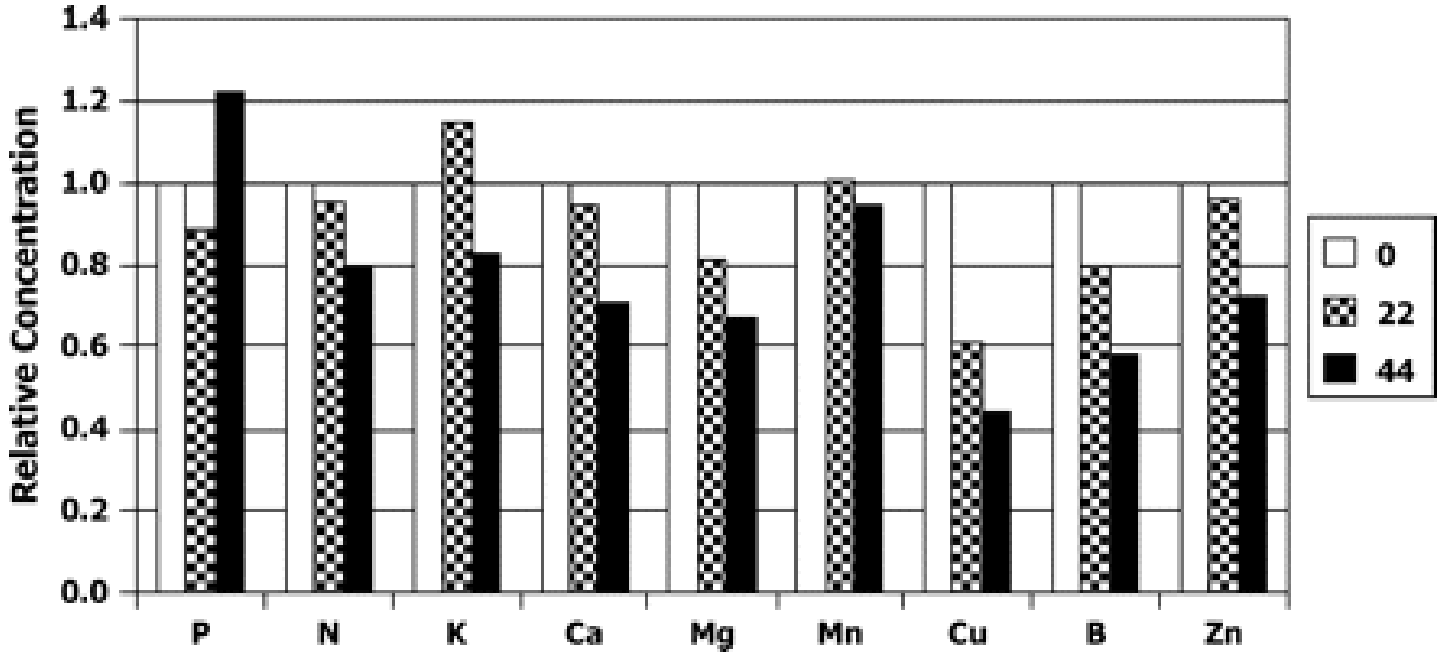
Every mineral, except phosphorus in fruits and vegetables (fertilizer) and sodium in dairy decreased significantly

- Trace minerals worst
- Cu down 77% in vegetables



Thomas D. A study on the mineral depletion of the foods available to US as a nation over the period 1940 to 1991. Nutr Health 2003;17:85-115

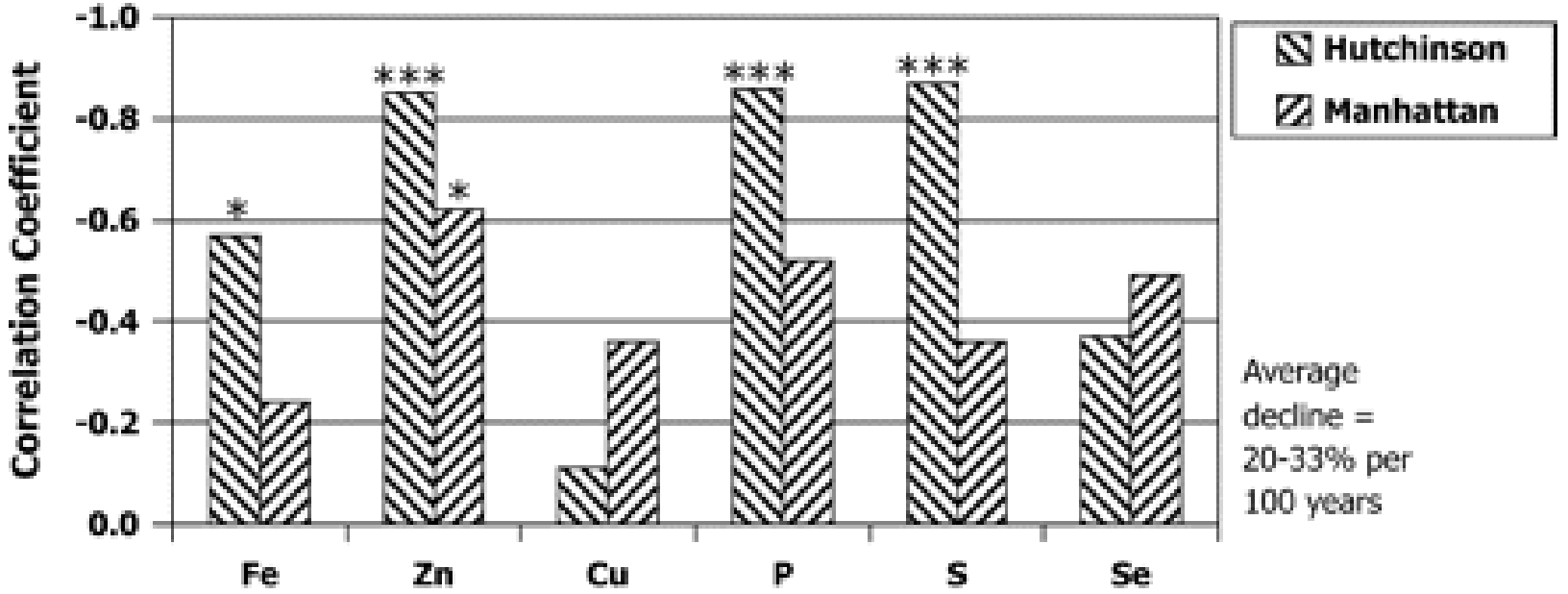
Fertilizers Decrease Nutrient Density



- Fertilizers make plants grow bigger causing “dilution effect”
- Red raspberry nutrient content decreases in proportion to use of high-phosphate fertilizers

Hughes M, Chaplin MH, Martin LW. Influence of mycorrhiza on the nutrition of red raspberries. HortScience 1979;14:521–523

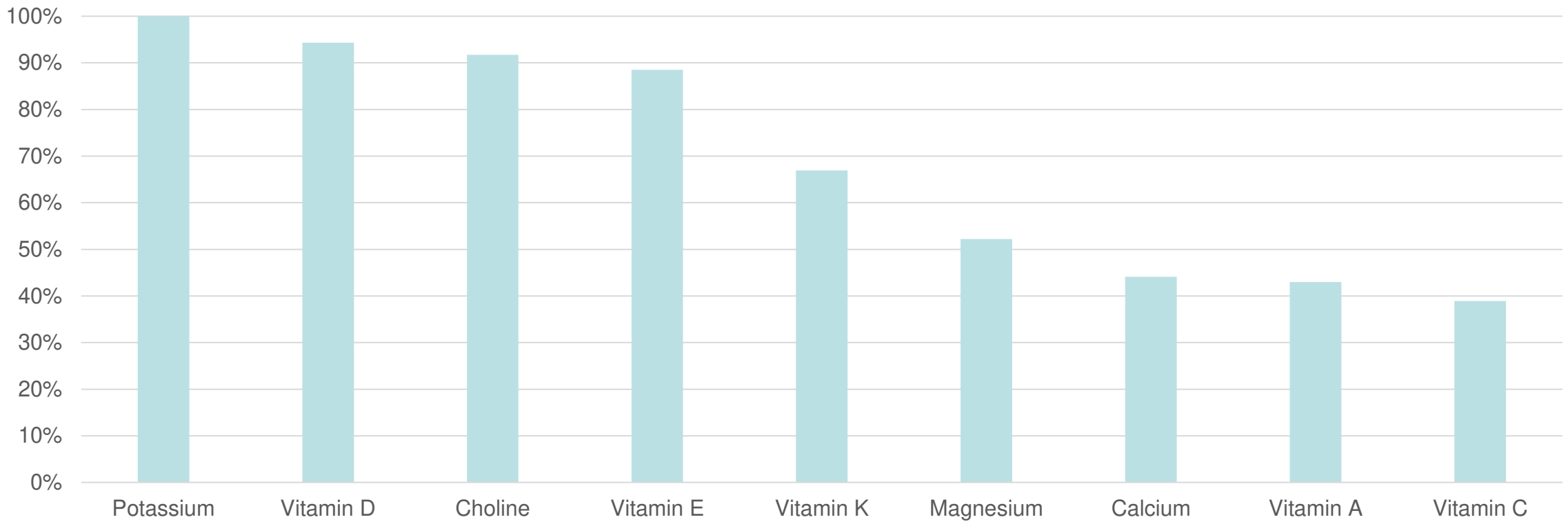
122 Years of Data!



- 14 varieties of hard red winter wheat
- 20-33% drop in minerals/100 years
- Strong inverse correlation with mineral content and size

Garvin DF, Welch RM, Finley JW. Historical shifts in the seed mineral micronutrient concentration of US hard red winter wheat germplasm. J. Sci. Food Agr. 2006;86:2213–20

Nutrient Deficiencies Rampant in USA



Wallace TC, McBurney M, Fulgoni VL 3rd. Multivitamin/mineral supplement contribution to micronutrient intakes in the United States, 2007-2010

Theme 2

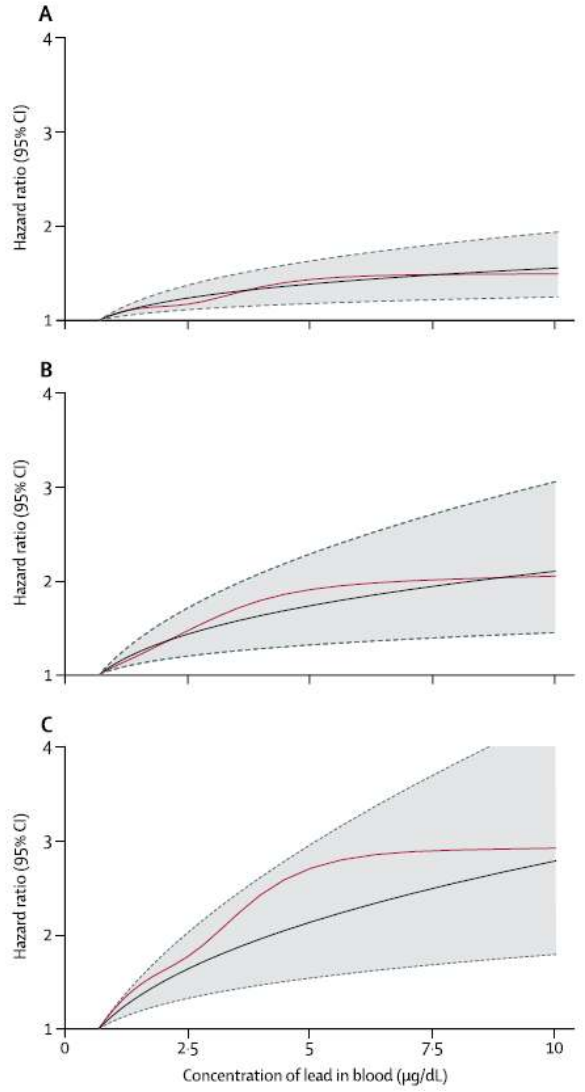
HIGH BODY LOAD OF TOXICANTS

Lead: Increases All-Cause Mortality & Death From Cardiovascular Disease

	Unadjusted HR (95% CI)	HR (95% CI)	Population attributable fraction (95% CI)	Avoidable deaths (95% CI)
All-cause mortality	3·79 (3·18–4·50)	1·37 (1·17–1·60)	18·0% (10·9–26·1)	412 000 (250 000–598 000)
Cardiovascular disease mortality	4·44 (3·47–5·68)	1·70 (1·30–2·22)	28·7% (15·5–39·5)	256 000 (138 000–352 000)
Ischaemic heart disease mortality	5·31 (4·06–6·93)	2·08 (1·52–2·85)	37·4% (23·4–48·6)	185 000 (116 000–241 000)

All models are adjusted for age (continuous and age-squared), sex, household income (<US$20 000 or ≥$20 000 per year), ethnic origin (white, black, or Mexican-American), body-mass index (normal [<25·0 kg/m²], overweight [25·0–29·9 kg/m²], or obese [≥30·0 kg/m²]), smoking status (never, current, or former), hypertension (systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg), urinary cadmium (tertiles [µg/g]), alcohol consumption (four or fewer or more than four drinks per month), physical activity in previous month (none, one to 14 times, 15 or more times), healthy eating index (tertiles), serum cholesterol (continuous), and glycated haemoglobin (continuous). Hazard ratios (HRs) for continuous concentrations of lead in blood represent the risk for an increase in log-transformed concentrations of lead in blood from 1·0 µg/dL to 6·7 µg/dL (0·048 µmol/L to 0·324 µmol/L (tenth to 90th percentiles).

***Table 2*: Adjusted HRs, population attributable fractions, and avoidable deaths from all causes, cardiovascular disease, and ischaemic heart disease in the NHANES-III mortality follow-up study (n=14 289)**

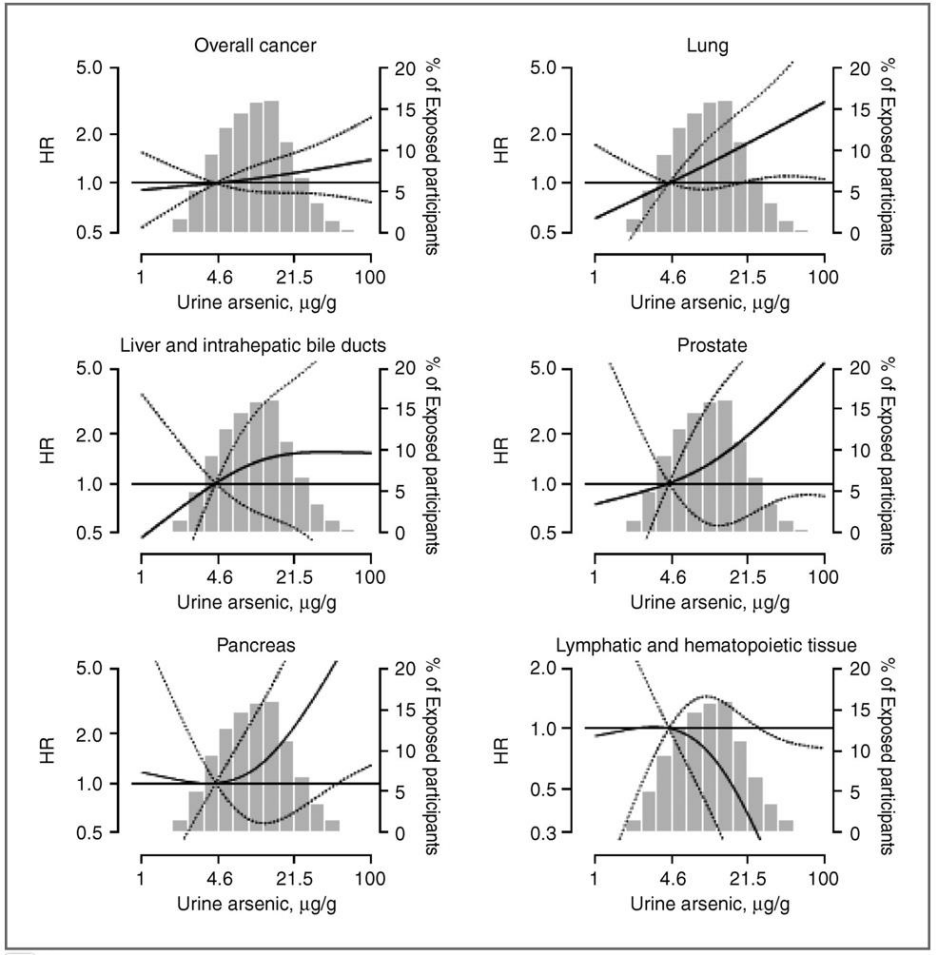


Lanphear BP, Rauch S2, Auinger P, et al. Low-level lead exposure and mortality in US adults: a population-based cohort study. Lancet Public Health. 2018 Apr;3(4):e177-e184. PMID: 29544878

Arsenic: Major Factor in Many Cancers

- 3,932 American Indians

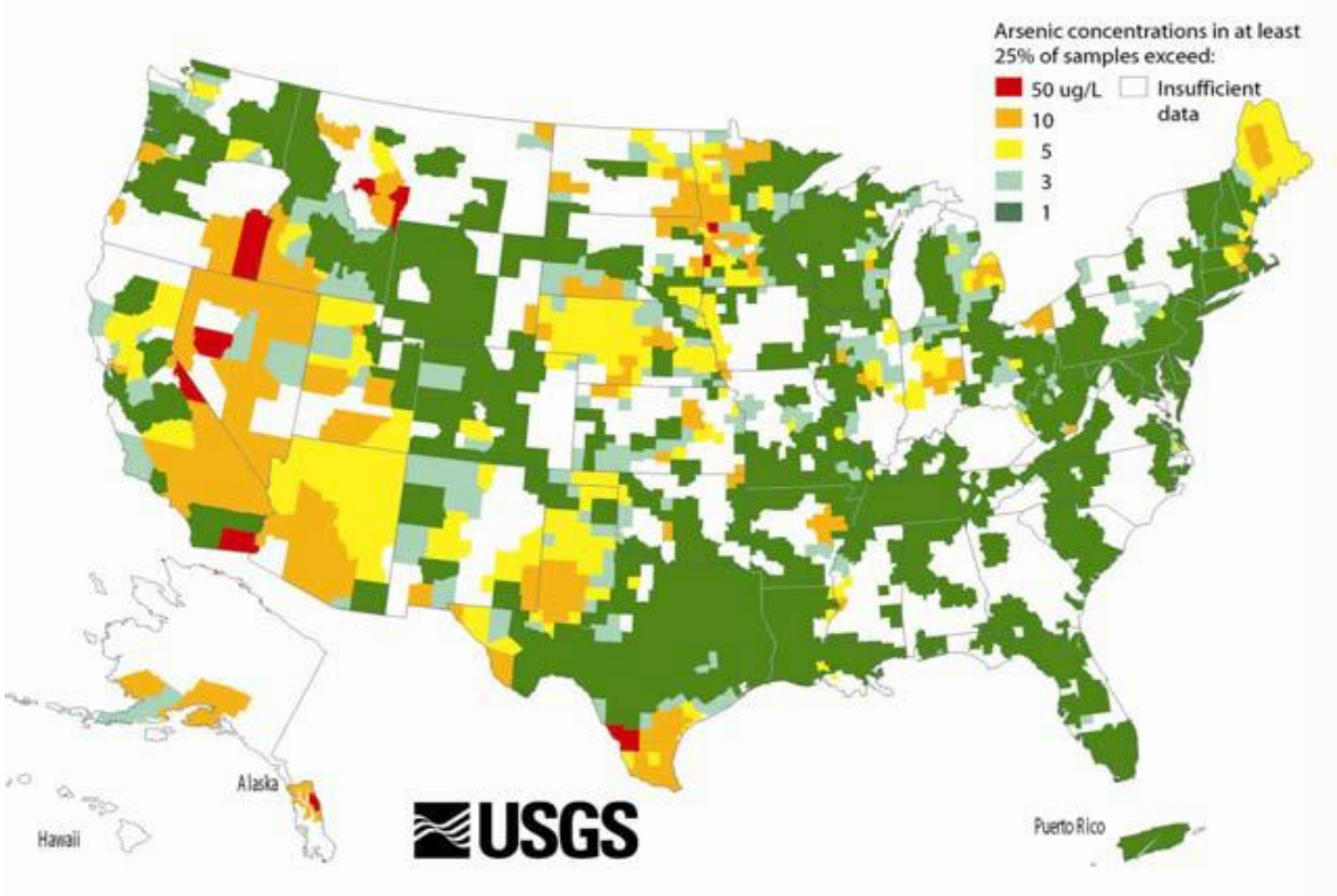
- Dose-dependent carcinogen
- Arseic dose-dependent correlation with:
  - Overall cancer risk
  - Cancers of lung, prostate, pancreas, liver
- Arsenic not associated with cancers of:
  - Esophagus, stomach, colon, rectum, breast
- Protective for blood cancers?
- Adjusted for age, sex, smoking status, BMI (kg/m2)



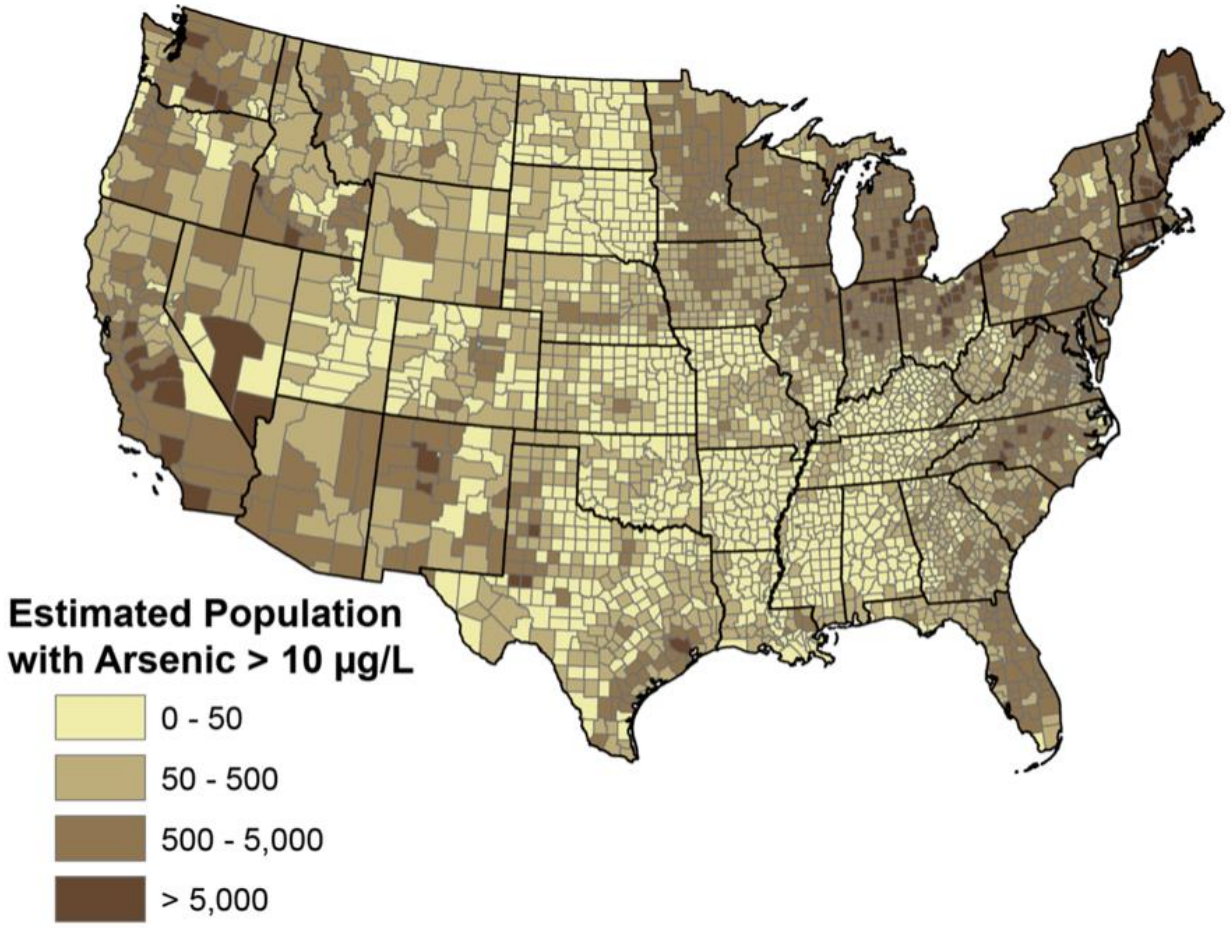
García-Esquinas E, Pollán M, Umans JG, et al. Arsenic exposure and cancer mortality in a US-based prospective cohort: the strong heart study. Cancer Epidemiol Biomarkers Prev. 2013 Nov;22(11):1944-53

Arsenic Contamination of US Water Supplies

- Only 50% of US public water supplies have reported their arsenic levels!

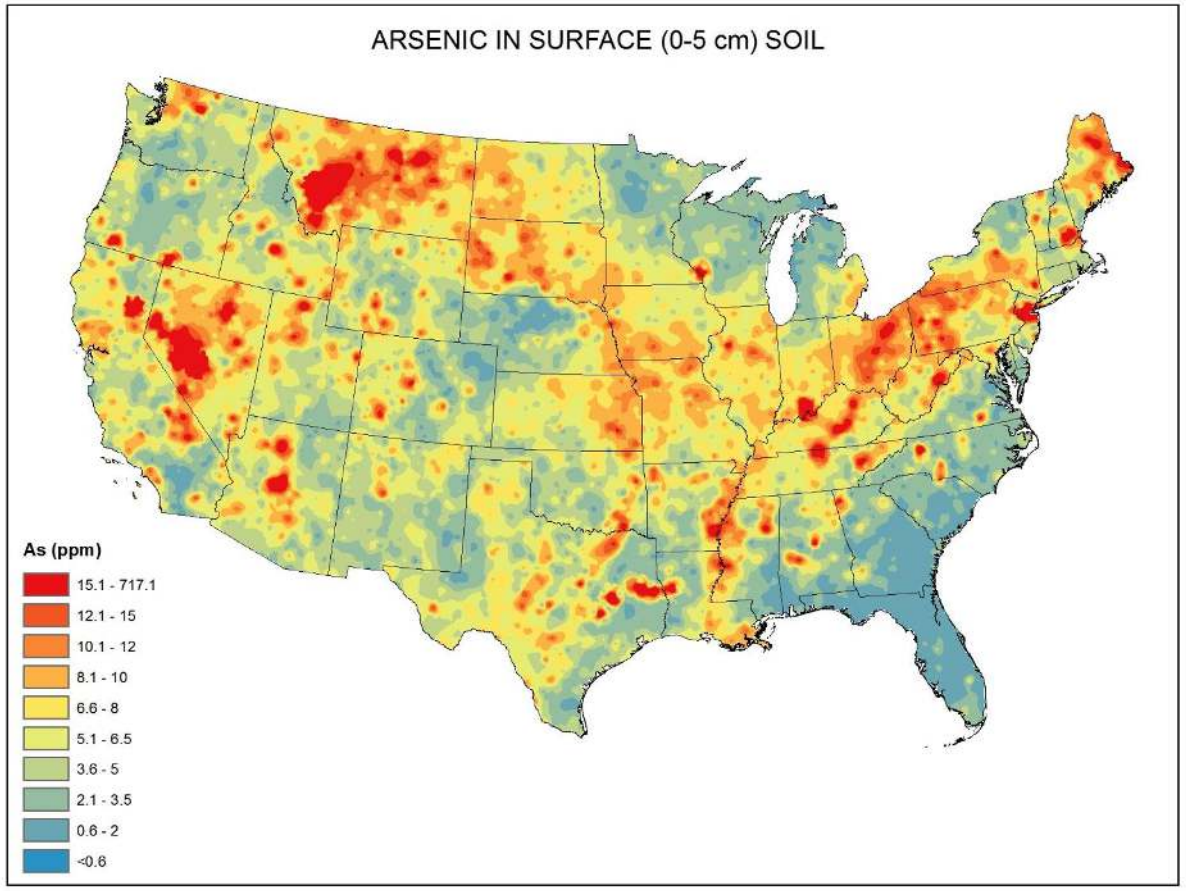


Arsenic Contamination of US Private Wells



Arsenic and Drinking Water. https://www.usgs.gov/mission-areas/water-resources/science/arsenic-and-drinking-water?qt-science_center_objects=0#qt-science_center_objects. Accessed March 9, 2020.

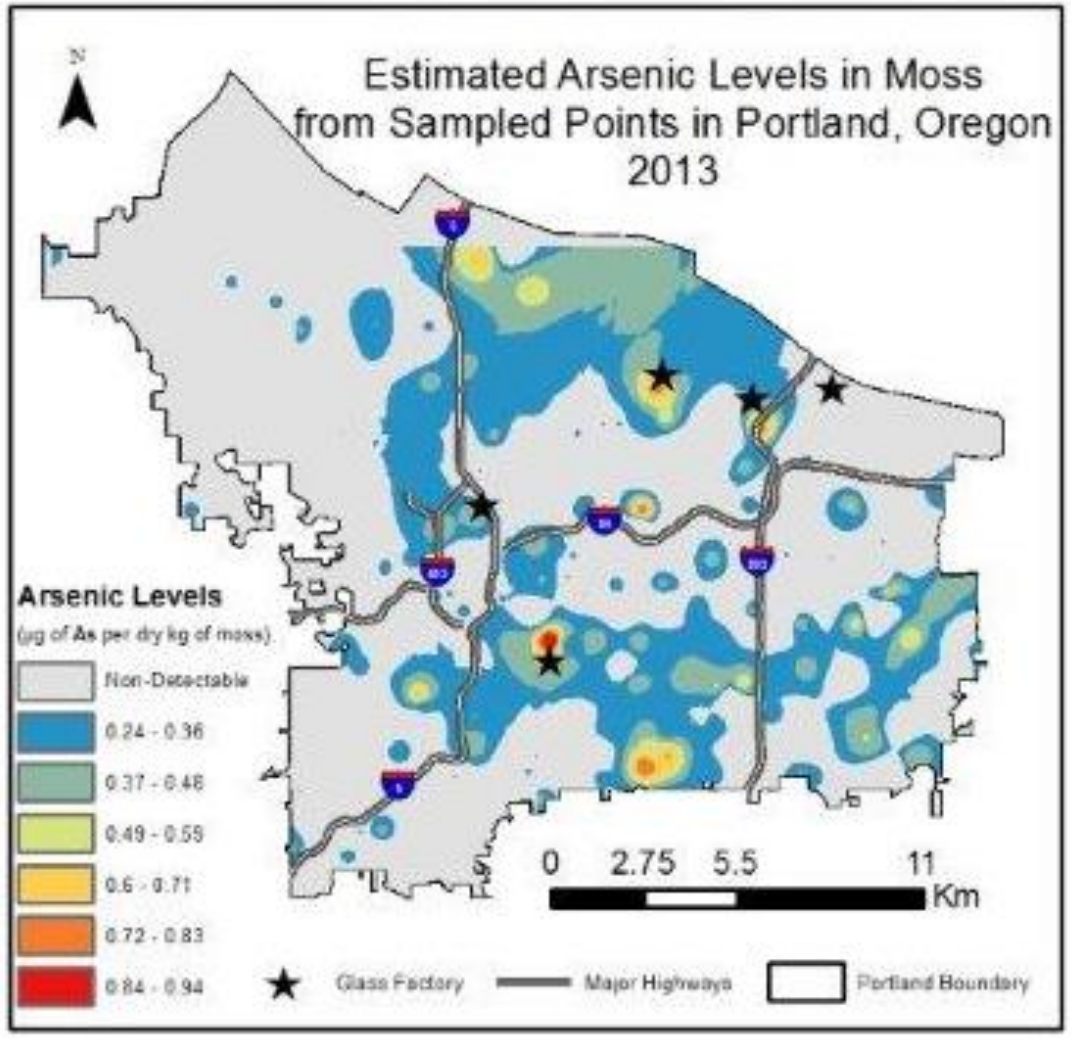
Arsenic Contamination of US Soil



Arsenic in Surface Soil. https://www.wired.com/wp-content/uploads/images_blogs/wiredscience/2013/09/As_0-5-cm_soil.jpg . Accessed February 24, 2020.

Portland Industrial Example

- Arsenic from colored glass manufacturing
- (Also releases a lot of cadmium into environment)



Arsenic Body Load

Urinary Total Arsenic (2003 – 2010)

CAS Number 7440-38-2

Geometric mean and selected percentiles of urine concentrations (in µg/L) for the U.S. population from the National Health and Nutrition Examination Survey.

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 (2003 - 2004)	8.30 (7.19-9.57)	7.70 (6.90-8.90)	16.0 (14.1-18.7)	37.4 (31.6-43.5)	65.4 (48.7-83.3)	2557
Total population (2005 - 2006)	9.29 (8.05-10.7)	8.65 (7.48-9.99)	17.1 (14.9-20.6)	41.1 (33.3-49.7)	66.7 (53.7-87.0)	2576
Total population (2007 - 2008)	8.10 (7.44-8.83)	7.49 (6.90-8.12)	14.9 (13.2-17.0)	33.3 (29.8-38.7)	50.8 (42.3-65.1)	2605
Total population (2009 - 2010)	9.28 (8.47-10.2)	8.15 (7.20-8.98)	18.0 (15.3-20.8)	44.6 (39.0-55.1)	85.6 (64.7-114)	2860

- Primary sources: water, chicken, rice
- Threshold for increased disease risk: 10.0 ug/L urine

⇒ >35% of US population exceeds threshold

D'Ippoliti D, Santelli E, De Sario M, Scortichini M, Davoli M, Michelozzi P. Arsenic in Drinking Water and Mortality for Cancer and Chronic Diseases in Central Italy, 1990-2010. PLoS One. 2015 Sep 18;10(9):e0138182. PMID: 2638385

https://www.cdc.gov/exposurereport/pdf/fourthreport.pdf 2015 update (accessed 9/1/2017)

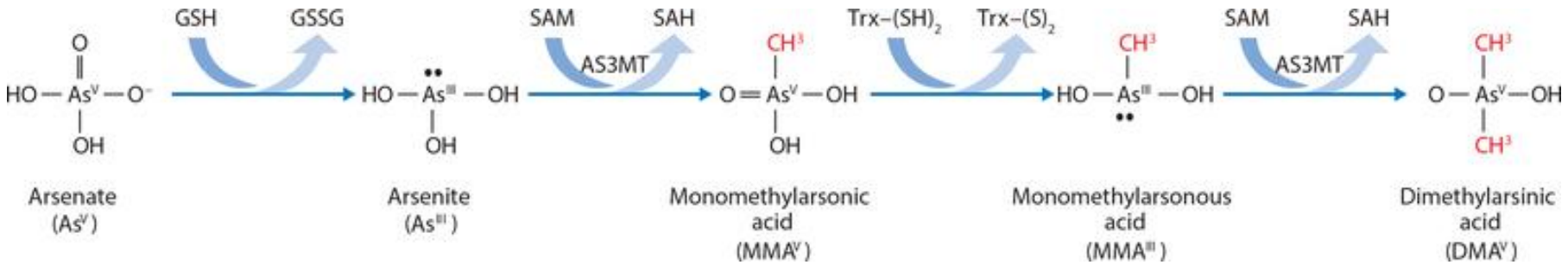
Nigra AE, Nachman KE, Love DC, Grau-Perez M, Navas-Acien A. Poultry Consumption and Arsenic Exposure in the U.S. Population. *Environ Health Perspect*. 2017;125(3):370–377. doi:10.1289/EHP351

deCastro BR, Caldwell KL, Jones RL, Blount BC, Pan Y, Ward C, Mortensen ME. Dietary sources of methylated arsenic species in urine of the United States population, NHANES 2003-2010. PLoS One. 2014 Sep 24;9(9):e108098. doi: 10.1371/journal.pone.0108098.

Toxicity of Common Forms of Arsenic in Humans

Species	Type	Half-Life	Primary Source	LD50
MMA	Organic	10-20 hrs	Food	2 mg/kg
Arsenate (V)	Inorganic	2-4 days	Water	8 mg/kg
Arsenite (III)	Inorganic	2–4 days	Water	26 mg/kg
DMA	Organic	10-20 hrs	Food	648 mg/kg
Arsenobetaine	Organic	4-6 hrs	Seafood	>4,000 mg/kg

Arsenic Metabolism - Multiple Key Enzymes



- MMA 8x **MORE** toxic than inorganic arsenic
- DMA 400x **LESS** toxic than inorganic arsenic
- Blood GSH inversely associated with arsenic in urine and blood

Bozack AK, Saxena R, Gamble MV. Nutritional influences on one-carbon metabolism: effects on arsenic methylation and toxicity. Annu Rev Nutr. 2018 Aug 21;38:401-429. PMID: 29799766

Genetics Hugely Important

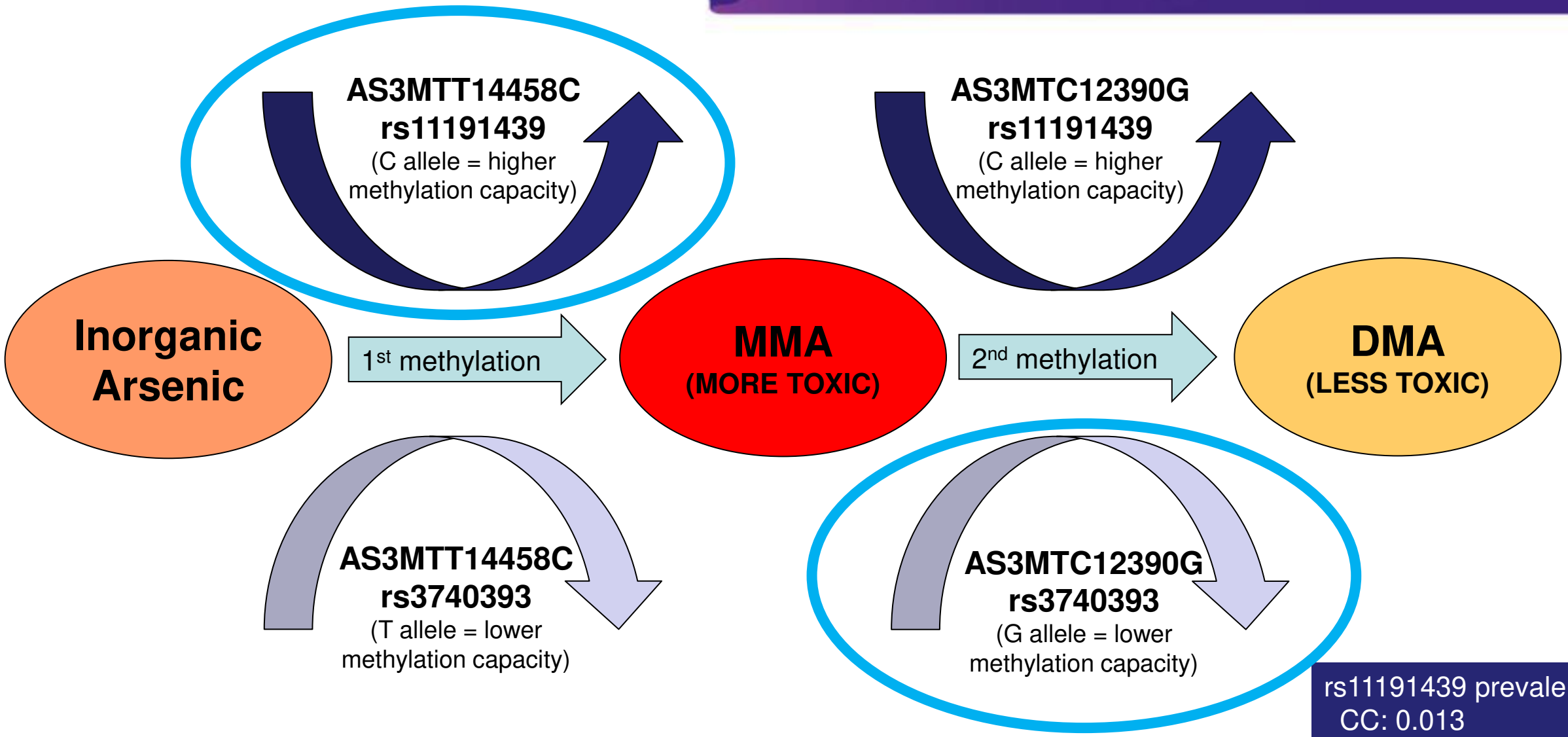
- C allele of AS3MT 14458 (rs11191439) higher 1st methylation capacity than T
- C allele of AS3MT 12390 (rs3740393) higher 2nd methylation capacity than G

- Fast 1st methylation + Slow 2nd methylation = **Greatly increased arsenic toxicity**

- 21% of population poorly detoxifies arsenic

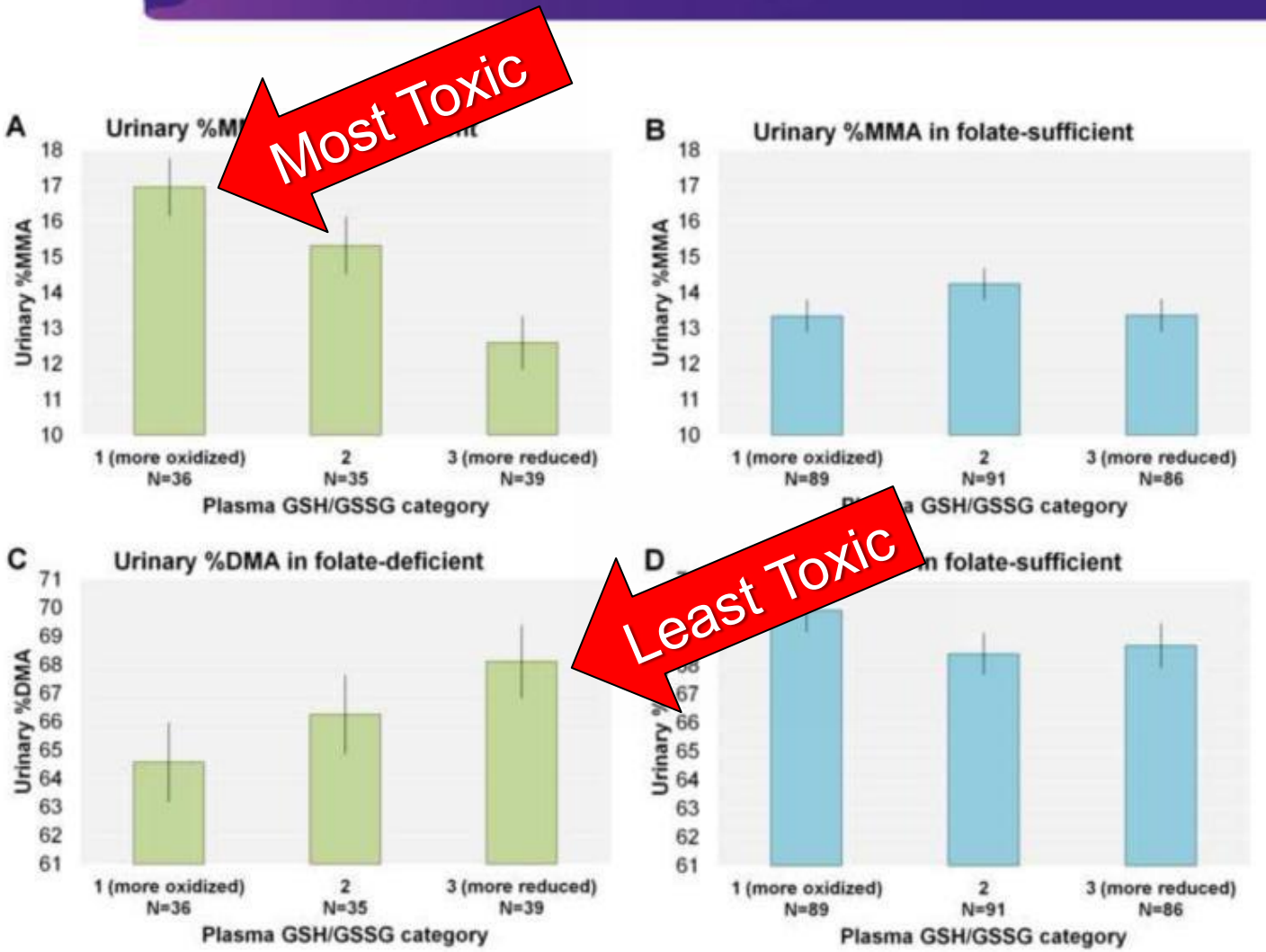
- 1% of population especially susceptible to arsenic damage

Agusa T, Fujihara J, Takeshita H, Iwata H. Individual variations in inorganic arsenic metabolism associated with AS3MT genetic polymorphisms. Int J Mol Sci. 2011;12(4):2351-8



rs11191439 prevalence
CC: 0.013
CT: 0.181
TT: 0.805

Reduced Glutathione Especially Important When Folate Deficient



Niedzwiecki MM, Hall MN, Liu X, et al. Interaction of plasma glutathione redox and folate deficiency on arsenic methylation capacity in Bangladeshi adults. Free Radic Biol Med. 2014 Aug;73:67-74

Huge Variability Detoxification Function

- CYP2D6
  - Metabolizes ~25% of common prescription drugs
  - 7 % of Caucasians poor metabolizers
  - ~30% ultra rapid metabolizers in Arabian and Eastern African populations
  - More adverse effects in poor metabolizers, and ineffective dosing in ultra-rapid metabolizers
  - Inhibited by ginger

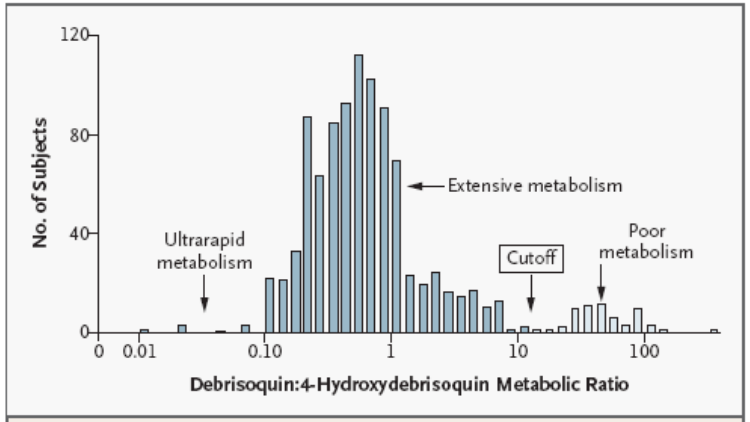


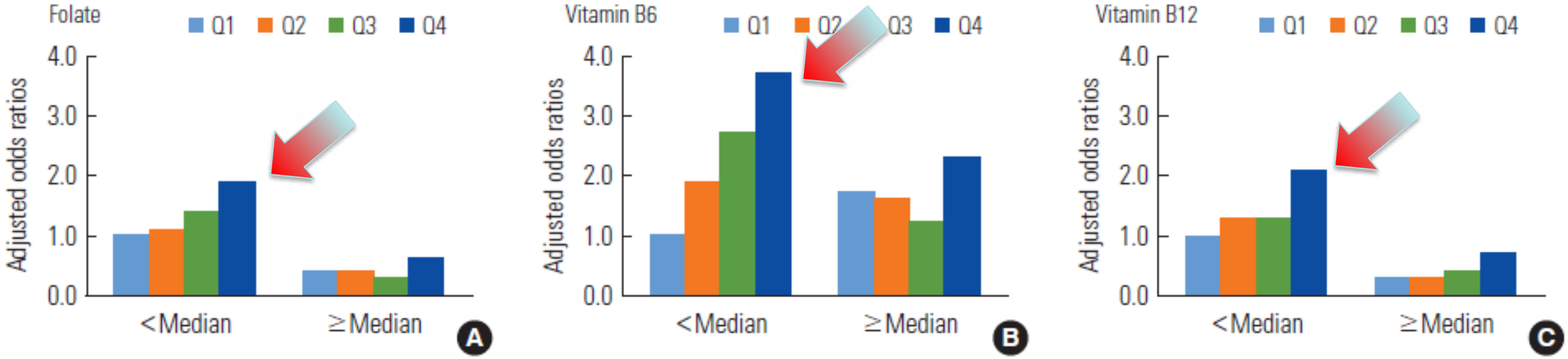
Figure 3. Pharmacogenetics of CYP2D6.
Urinary metabolic ratios of debrisoquin to its metabolite, 4-hydroxydebrisoquin, are shown for 1011 Swedish subjects. The Cutoff box indicates the cutoff point between subjects with poor metabolism as a result of decreased or absent CYP2D6 activity and subjects with extensive metabolism. Modified from Bertilsson et al.[17] with the permission of the publisher.

Desta Z, et al. Clinical significance of the cytochrome P450 2C19 genetic polymorphism. Clin Pharmaco 2002
Sim SC, et al. A common novel CYP2C19 gene variant causes ultrarapid drug metabolism relevant for the drug response to proton pump inhibitors and antidepressants. Clin Pharmacol Ther. 2006
Wilkinson GR. Drug metabolism and variability among patients in drug response. N Engl J Med. 2005
Kirchheiner J, et al. Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. Pharmacogenomics J. 2007

Theme 3

TOXINS AND NUTRIENT DEFICIENCIES SYNERGISTICALLY INCREASE DAMAGE

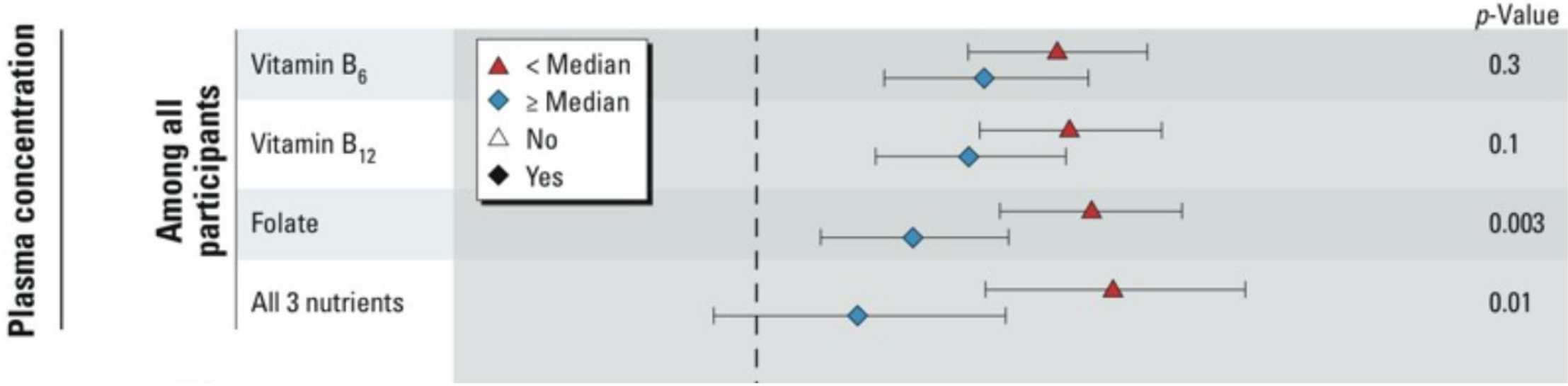
LEAD INCREASES NEED FOR B-VITAMINS: HYPERHOMOCYSTEINEMIA



Deficiencies in folate, B6 or B12 make lead more toxic!
Lead aggravates damage from low B-vitamins

Lee YM. Et al. Association of homocysteine levels with blood lead levels and micronutrients in the US general population. J Prev Med Public Health. 2012 Nov;45(6):387-93

NUTRIENT DEFICIENCY AGGRAVATES LEAD TOXICITY



Supplement users more protected from lead
Best protection when both nutrient-rich diet AND supplements—BUT dietary more effective

Bakulski KM, Park SK, Weisskopf MG, et al. Lead exposure, B vitamins, and plasma homocysteine in men 55 years of age and older: the VA normative aging study. Environ Health Perspect. 2014 Oct;122(10):1066-74

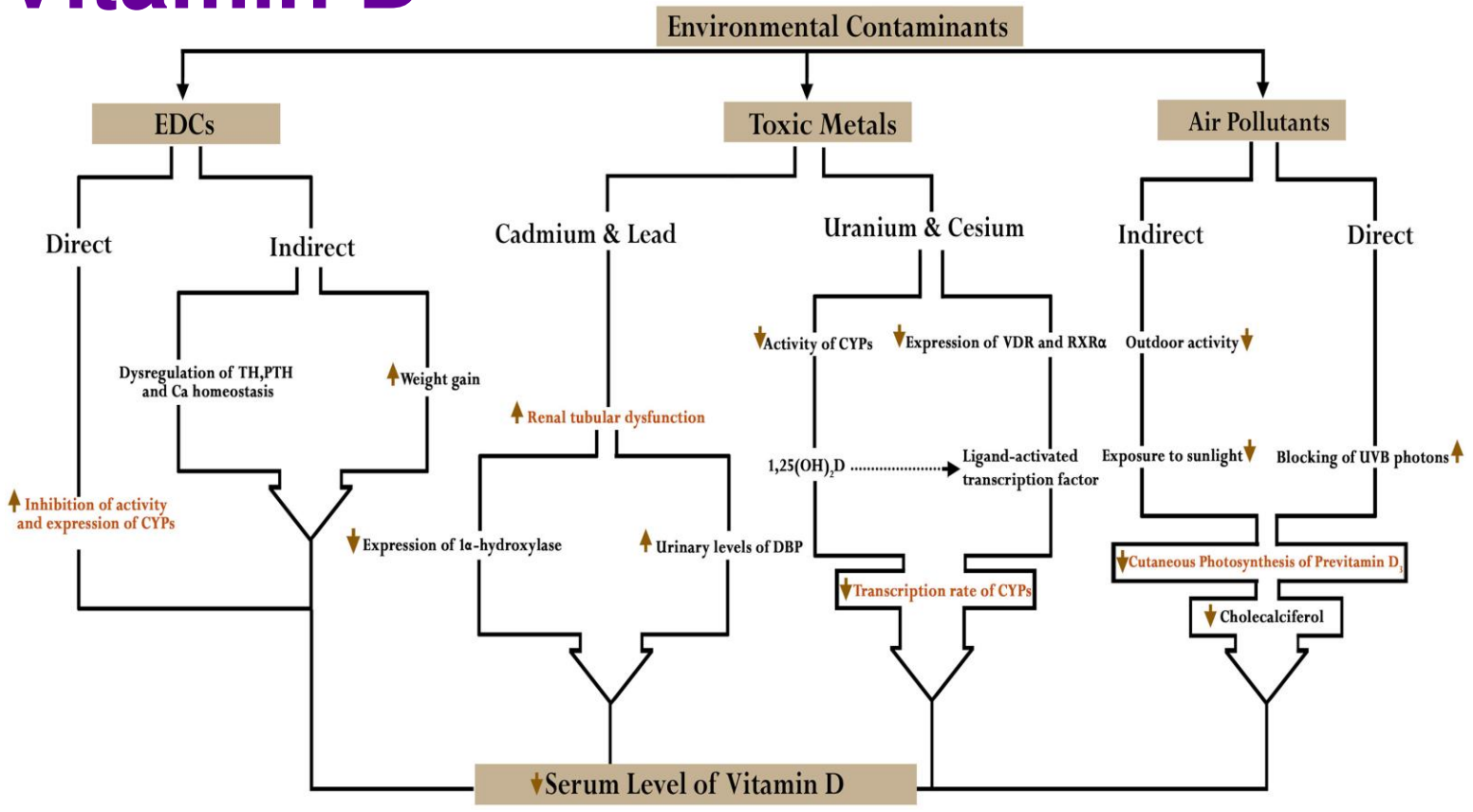
TOXINS IN SOIL DECREASE MINERALS AND VITAMINS IN FOOD

Arsenic: ↓ Mn, Fe, Mg, K, P
Cadmium: ↓ 62% vitamin A; ↓ 75% vitamin C; ↓ Zn
Glyphosate: ↓ Mn

Khan A, Khan S, Khan MA, Qamar Z, Waqas M. The uptake and bioaccumulation of heavy metals by plants, their effects on plant nutrients, and associated health risk: a review. *Environmental Science and Pollution* Research. 2015; 22(18): 13772-13799
Widowati H. The influence of cadmium heavy metal on vitamins in aquatic vegetables. Makara Journal of Science. 2012; 16(1): 33-38

Endocrine Disrupting Chemicals, Toxic Metals, Air Pollutants Decrease Vitamin D

- Pesticides, BPA, phthalates, polyhalogenated compounds
- Cadmium, lead
- Ozone, tobacco, polycyclic aromatic hydrocarbons (PAHs)

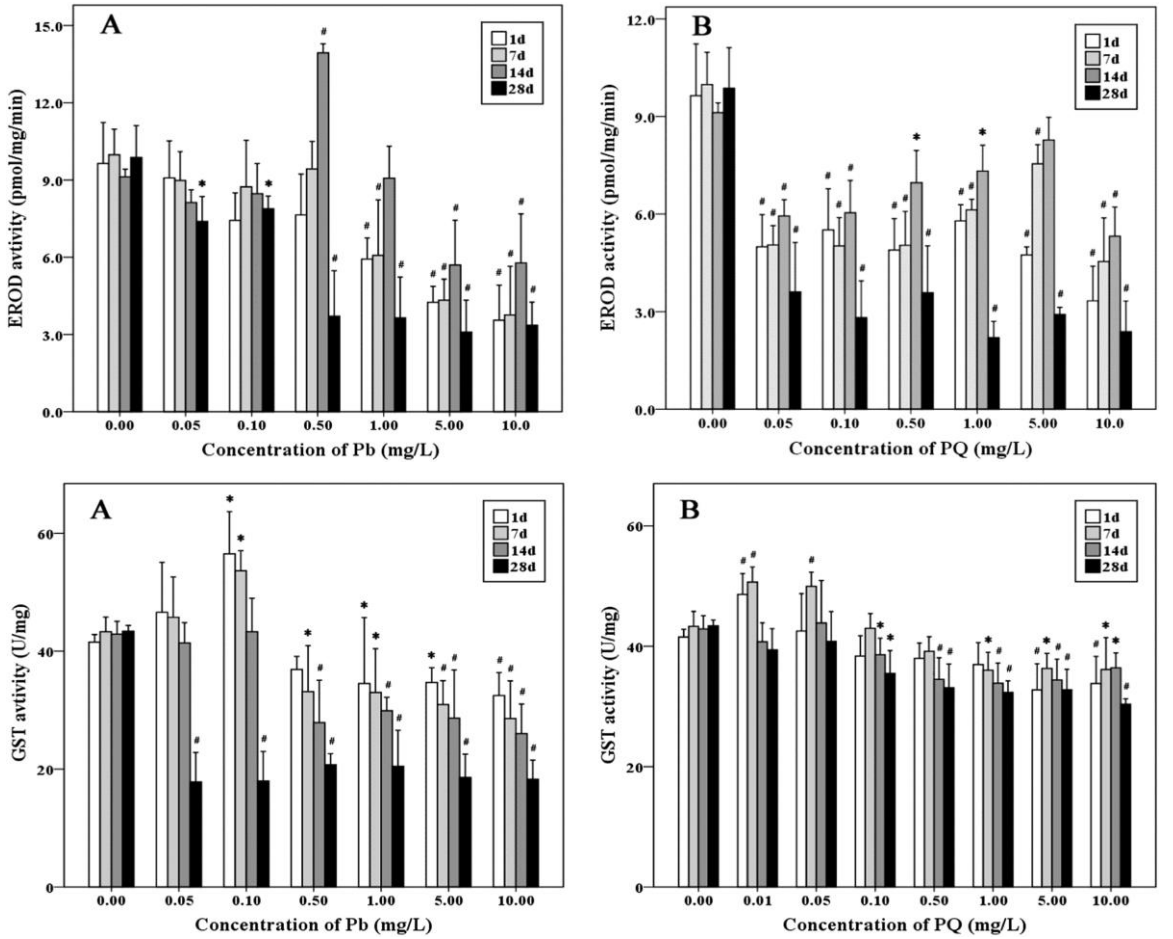


Mousavi SE, Amini H, Heydarpour P, et al. Air pollution, environmental chemicals, and smoking may trigger vitamin D deficiency: Evidence and potential mechanisms. Environ Int. 2019 Jan;122:67-90 PMID: 30509511

Toxins Impair Detoxification Systems

- Animal study (goldfish)
- Heme is core of CYPs

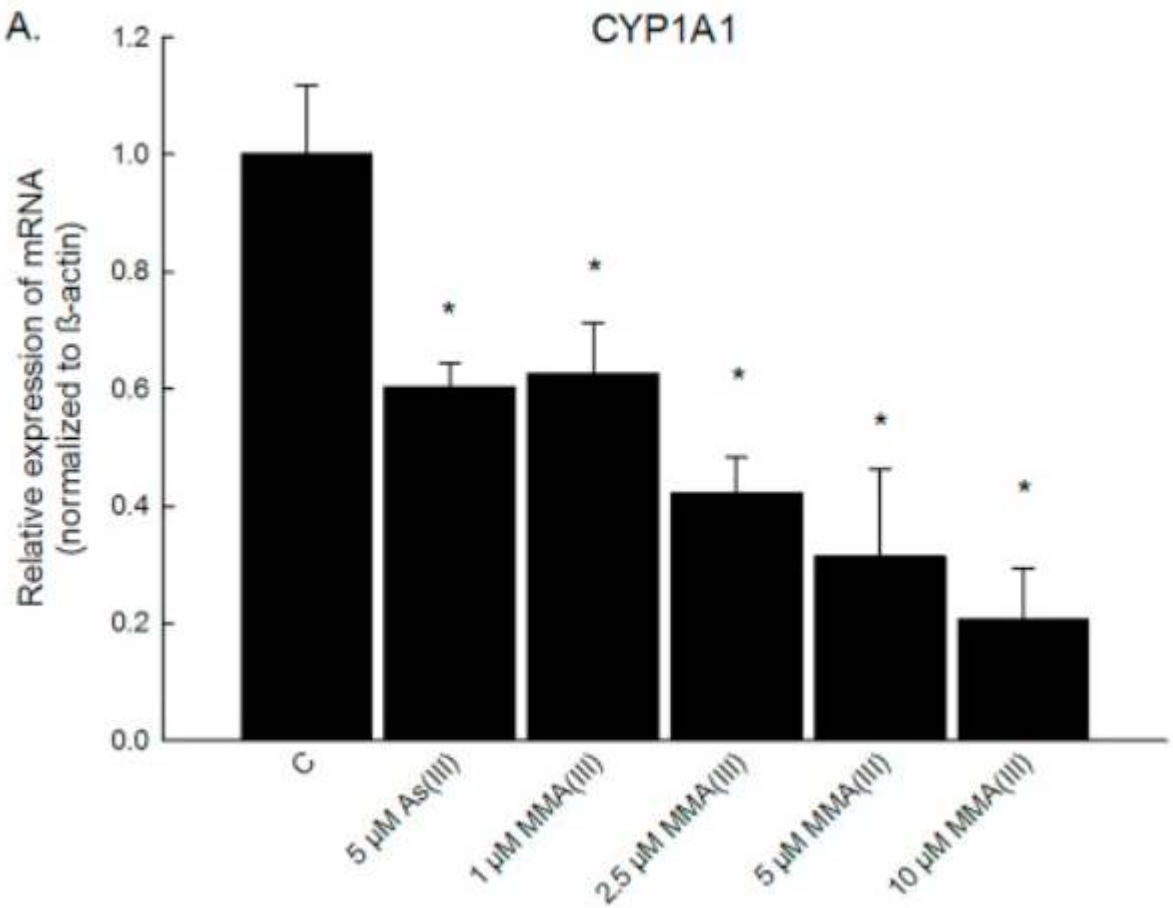
- Lead (Pb) and paraquat (PQ) decrease both Phase I and Phase II detoxification enzymes
- Worse when also iron deficient



Xu X, Cui Z, Wang X, et al. Toxicological responses on cytochrome P450 and metabolic transferases in liver of goldfish (Carassius auratus) exposed to lead and paraquat. Ecotoxicol Environ Saf. 2018 Apr 30;151:161-169

Arsenic Decreases CYP Induction

- Human cell culture
- Arsenic blocks enzyme induction
- Note that MMA much more damaging than elemental arsenic

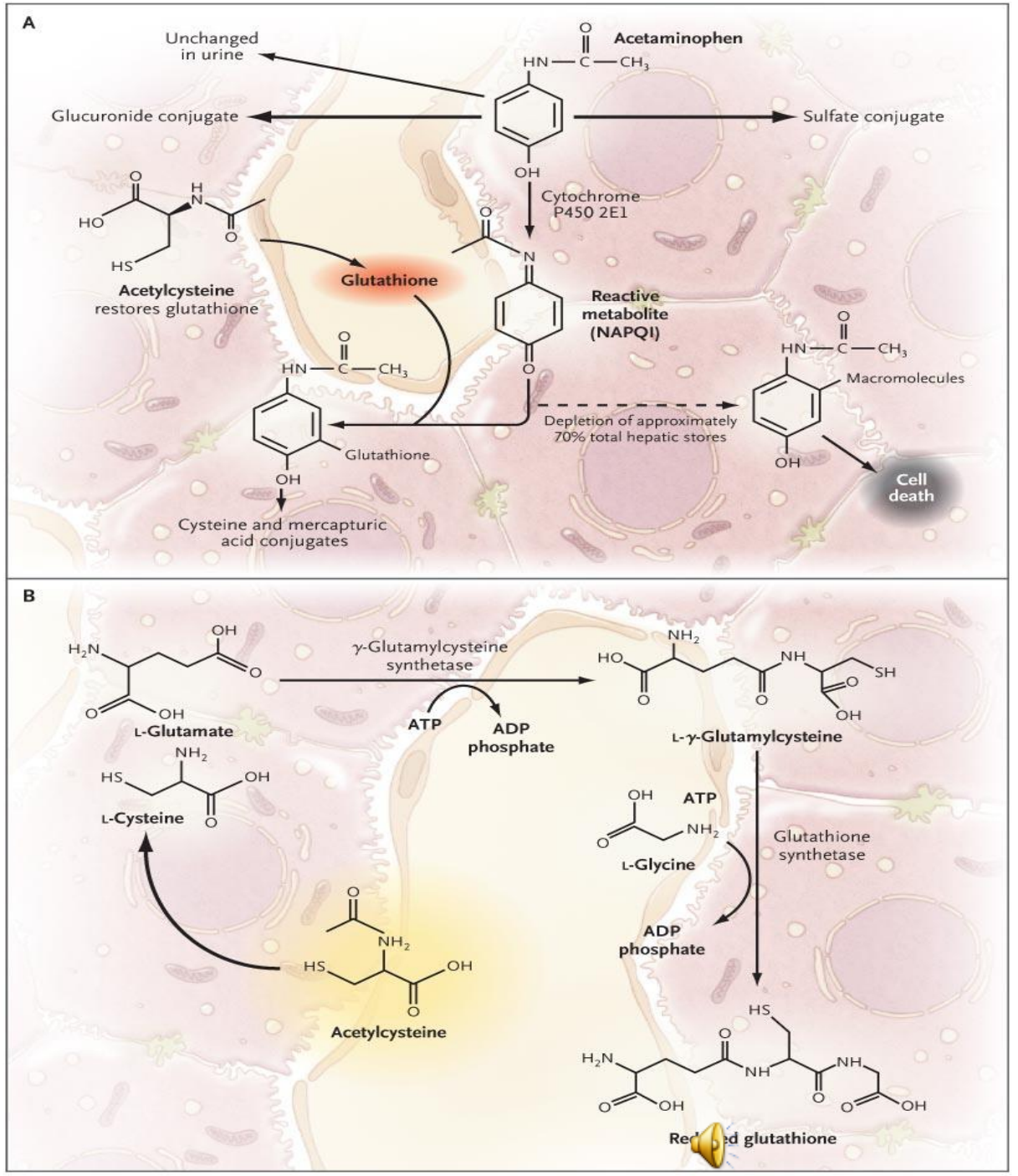


Elshenawy OH, Abdelhamid G, Soshilov AA, et al. Down-regulation of cytochrome P450 1A1 by monomethylarsonous acid in human HepG2 cells. Toxicol Lett. 2017 Mar 15;270:34-50 PMID: 28189647

Theme 4

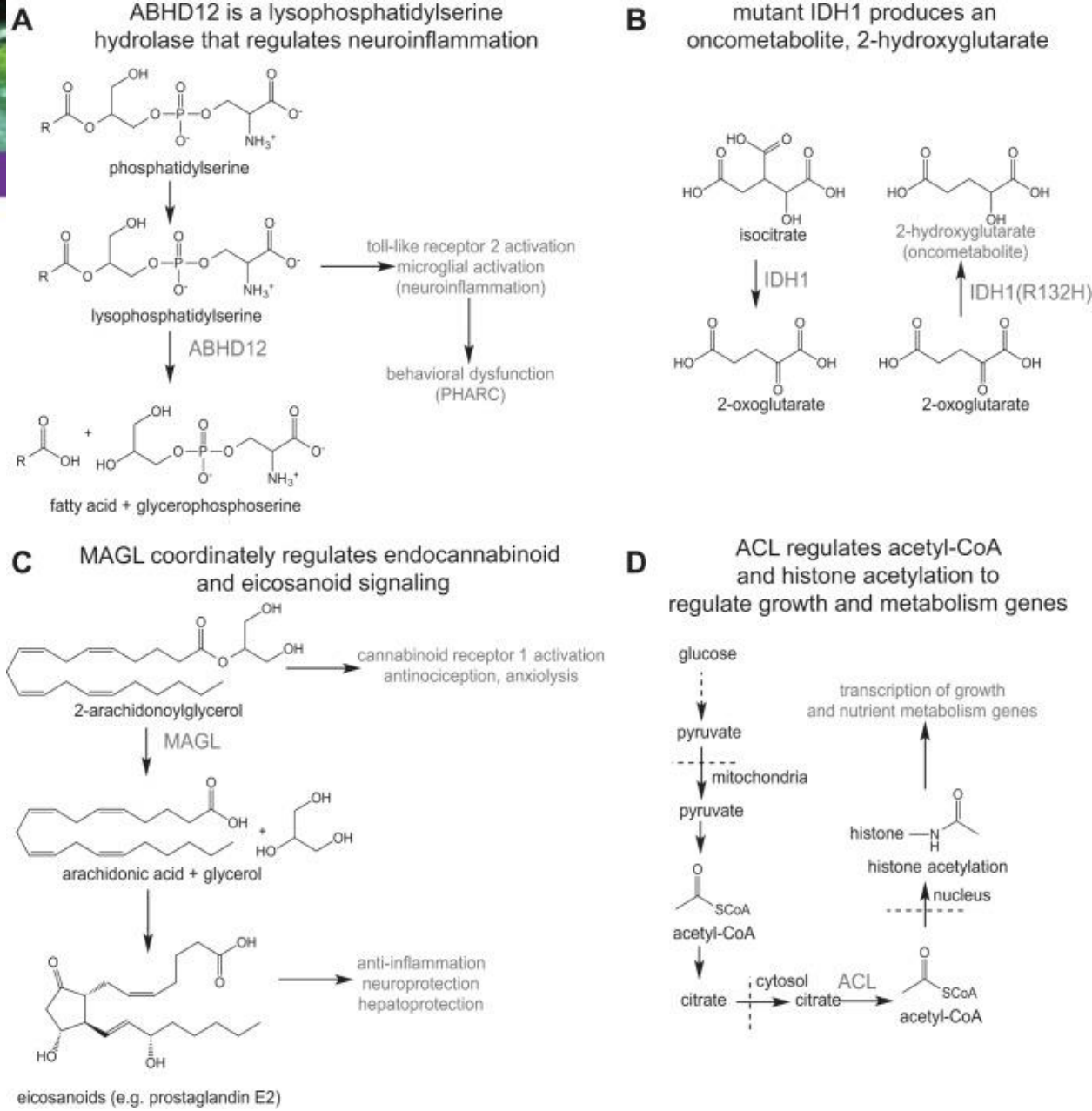
HUMAN PHYSIOLOGY IS A MASSIVELY PARALLEL MATRIX, NOT SIMPLY SINGLE PATHWAYS

Detoxification of Acetaminophen Clear Example of Multiple Pathways



Reductionistic View of Biochemistry Misses A Lot

- MANY plant molecules are now shown to have substantial physiological effects **independent of previously discovered biochemistry**
- Cannabinoid pathway classic example



Mulvihill MM, Da Nomura DK. Metabolomic Strategies to Map Functions of Metabolic Pathways. Am J Physiol Endocrinol Metab. 2014; 307 (3), E237-44 PMID: 24918200

Theme 5

MODERN AGRICULTURE DANGEROUSLY DISTORTS THE FOOD SUPPLY

WHAT ABOUT ALL THOSE OTHER MOLECULES?

Subtle and Often Unexpected Impact of "Unimportant" Constituents

- **Concept**: when plants are hybridized to increase one class of molecules, then there is decreased production of the others

- **Concept**: When foods are refined, the levels of many "unimportant" constituents decline

How Many Molecules in Food?

- Humans consume many grams everyday of molecules in food not considered “important”
- Many of these phytochemicals are bioactive beyond our current understanding because they act through weak biological feedback mechanisms, difficult to detect in vitro or considered involved in minor unimportant pathways
- 50,000 molecules identified; 200,000 projected

Hounsome N, Hounsome B, Tomos D, Edwards-Jones G. Plant metabolites and nutritional quality of vegetables. J Food Sci. 2008 May;73(4):R48-65 PMID: 18460139

The Food Supply has Changed Dramatically

- Hybridization
- GMO
- Growth induced with chemicals
- Plants are now so weak they need toxic chemicals to protect from insects, viruses, mold, etc.
- Farming costs decreased by spraying fields with herbicides to control weeds and pesticides to protect against organisms the foods have lost the ability to resist

Plant Molecules

- Anti-bacterial, anti-fungal, anti-viral
- Anti-insect
- Anti-herbivore
- Anti-oxidant
- Etc.

⇒ Organically-grown, heirloom plants are more resilient and need less help against pests

⇒ **Humans eating these plant molecules are more resilient and less susceptible to pests**

Zaynab M, Fatima M, Abbas S, et al. Role of secondary metabolites in plant defense against pathogens. Microb Pathog. 2018 Nov;124:198-202
PMID: 30145251

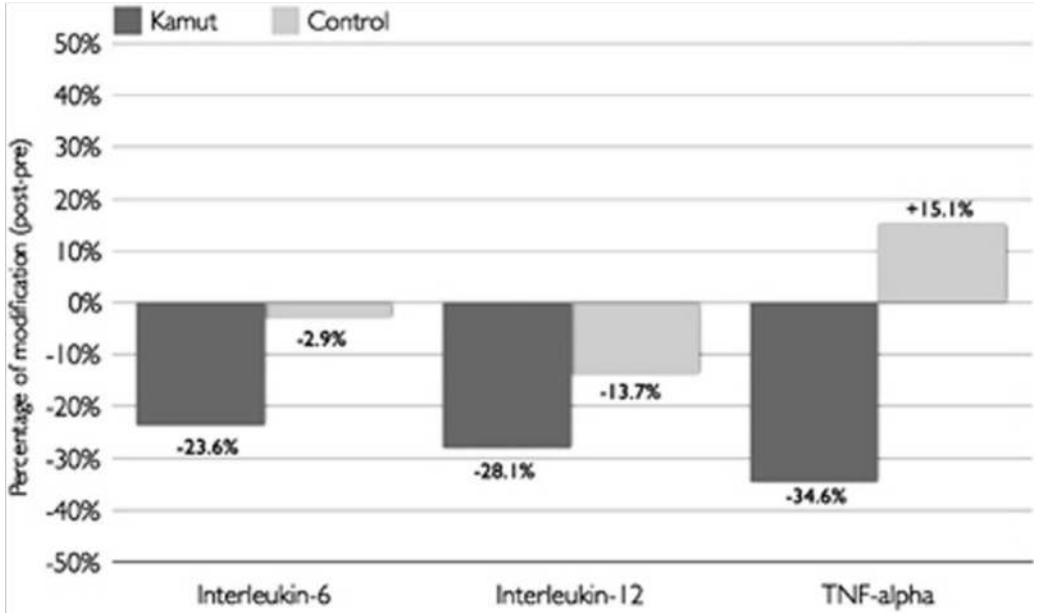
Ancient Kamut Compared to Current Wheat

- Crossover clinical study

- Much higher mineral levels:
  - Zinc: 64.7% higher
- Much lower inflammation:
  - TNF-alpha 49.7% lower
- Also lower cholesterol, LDL, blood sugar, etc.

Mineral element composition of Kamut and control wheat

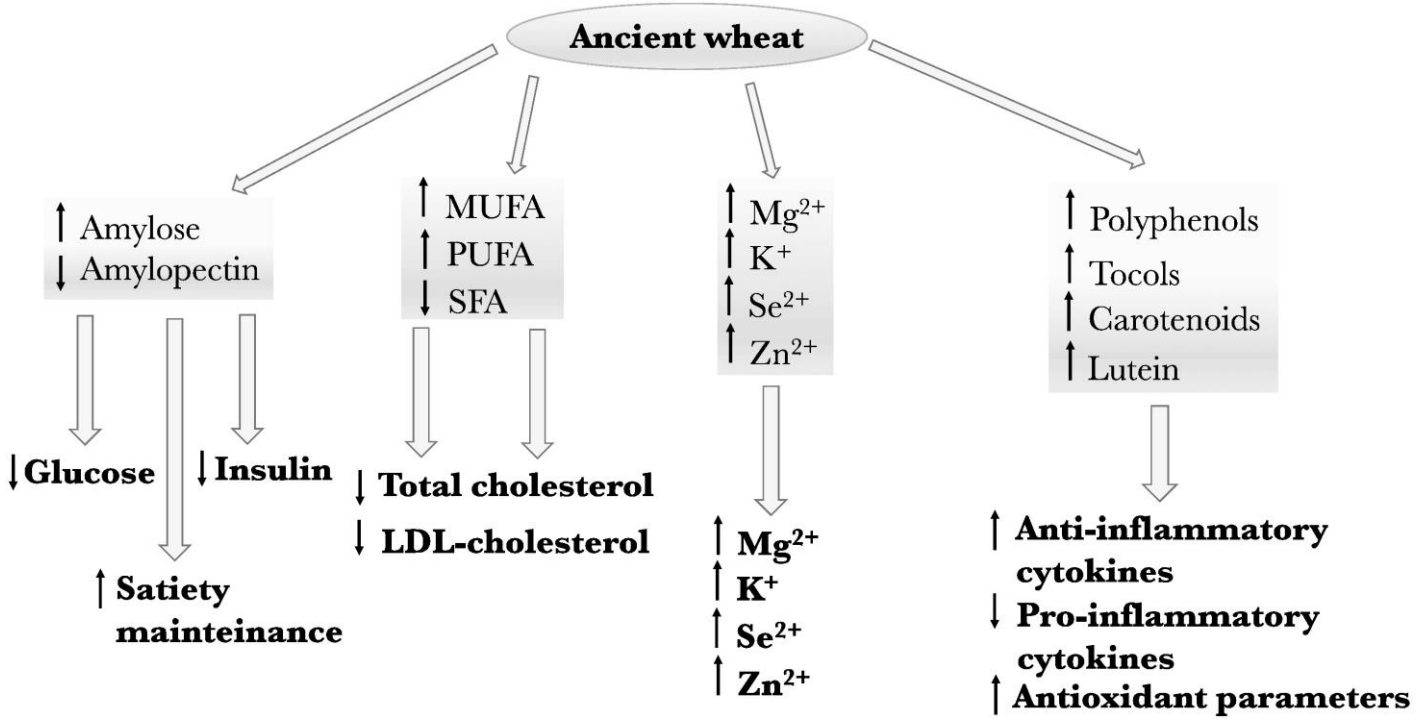
Variable (mg/kg)	*Kamut (Semolina)*	*Control (Semolina)*	P-value	*Kamut (Flour)*	*Control (Flour)*	P-value
Potassium	2817±6.52	2393±0.808	0.006	2663±0.811	1553±6.47	0.001
Magnesium	909.57±58.7	795.58±50.1	0.003	889.03±27.6	542.06±28.9	0.001
Phosphorus	2.98±0.26	2.67±0.62	0.001	2.85±0.62	1.77±0.84	0.02
Zinc	25.19±0.05	25.99±0.09	0.02	24.95±0.02	15.15±0.05	0.001
Iron	29.63±0.24	28.02±0.04	0.06	24.13±0.04	20.42±0.14	0.01
Selenium	0.99±0.04	0.92±0.03	0.2	0.90±0.008	0.74±0.006	0.02
Vanadium, mg/kg	1.01±0.02	0.73±0.008	0.005	0.98±0.008	0.63±0.004	0.0001



Sofi F, Whittaker A, Cesari F, et al. Characterization of Khorasan wheat (Kamut) and impact of a replacement diet on cardiovascular risk factors: cross-over dietary intervention study. Eur J Clin Nutr. 2013 Feb;67(2):190-5 PMID: 23299714

Ancient Wheat Healthier than Modern Wheat

- Emmer, einkorn, spelt, khorasan and various regional Italian varieties
- Higher in multiple nutrients: phytosterols, alkylresorcinols, minerals, etc.
- Real clinical impact (many human studies)



⇒ **Heirloom seeds**

Dinu M, Whittaker A, Pagliai G, et al. Ancient wheat species and human health: Biochemical and clinical implications. J Nutr Biochem. 2018 Feb;52:1-9 PMID: 29065353

Example Plant Metabolites Important to Human Health

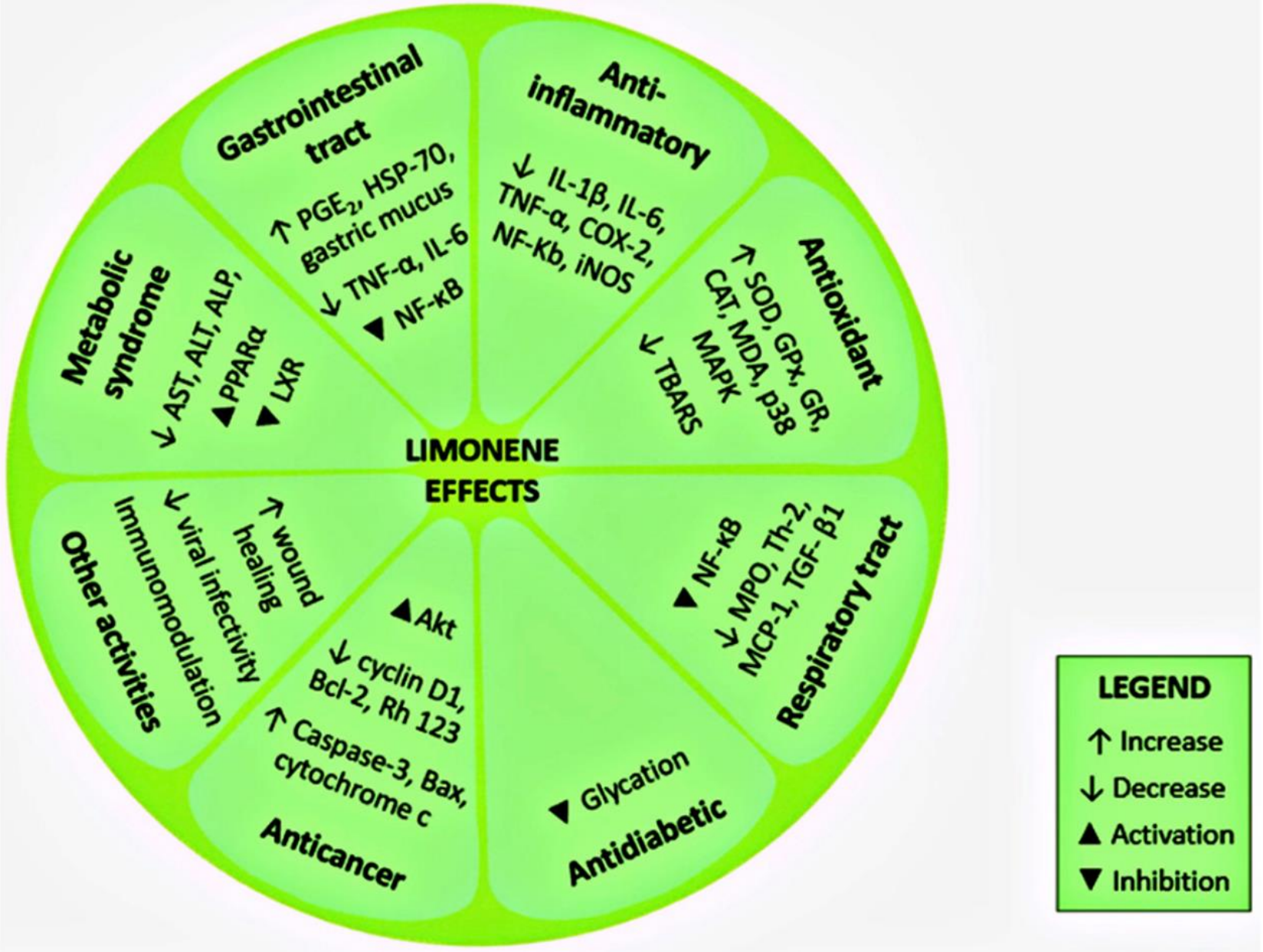
List of plant secondary metabolites against Insects. Listed secondary metabolites are shown their linked to a specific category and their target insect in specific plan.

Secondary Metabolites	Plants	Categories	Resistance against	Reference
Terpenoids	Citrus	Terpenoid Limonene	*Atta cephalotes*	[57]
	Pine and fir	Monoterpenes	*bark beetle*	[58]
Steroids	Common fern	Phytoecdysones	*Insect*	[59]
Terpenoids	Tobbaco	Trans-anethole and thymol, citronellal,	*Spodoptera litura*	[60]
Phenolics	Wheat	Phenolics	*Rhopalosiphum padi*	[61]
Phenolics	Willow plant	Phenolics	*Galerucella lineola*	[62]
Benzoic acid	Salix	Benzoic acid	*Operophtera brumata*	[63]
Phenolics	Strawberry	Phenolics	*Tetranychus urticae*	[64]
Phenolics	Cotton	Gossypol	*Heliothis virescens, Heliothis zea*	[65]
Alkaloids	Nightshade potato	Alkaloid demissine	*Leptinotarsa decemlineata*	[66]
Benzoxazinoides	Gramineae	DIMBOA	*Ostrinia nubilalis*	[67]
Cyanogenic Glucosides	Cassava	CNglcs	*Cyrtomenus bergi*	[68]
Cyanogenic Glucosides	Bitter almond plants	Amygdalin and prunasin	*Capnodis tenebronis*	[69]
Cyanogenic Glucosides	Trifolium repens	Amygdalin and prunasin	*Hypera postica*	[70]
Cyanogenic Glucosides	Lotus	Cyanogenic glucosides	*Zygaena filipendulae*	[71]
Cyanogenic Glucosides	P.lunatus	CNglcs	*Spodoptera eridania*	[73]

Zaynab M, Fatima M, Abbas S, et al. Role of secondary metabolites in plant defense against pathogens. Microb Pathog. 2018 Nov;124:198-202 PMID: 30145251

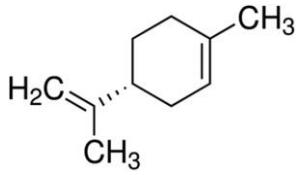
Terpenoids

- Carvacrol, linalool, and limonene
- Limonene most common terpenoid
- MANY beneficial physiological effects
- Terpenes active constituents in many herbal medicines

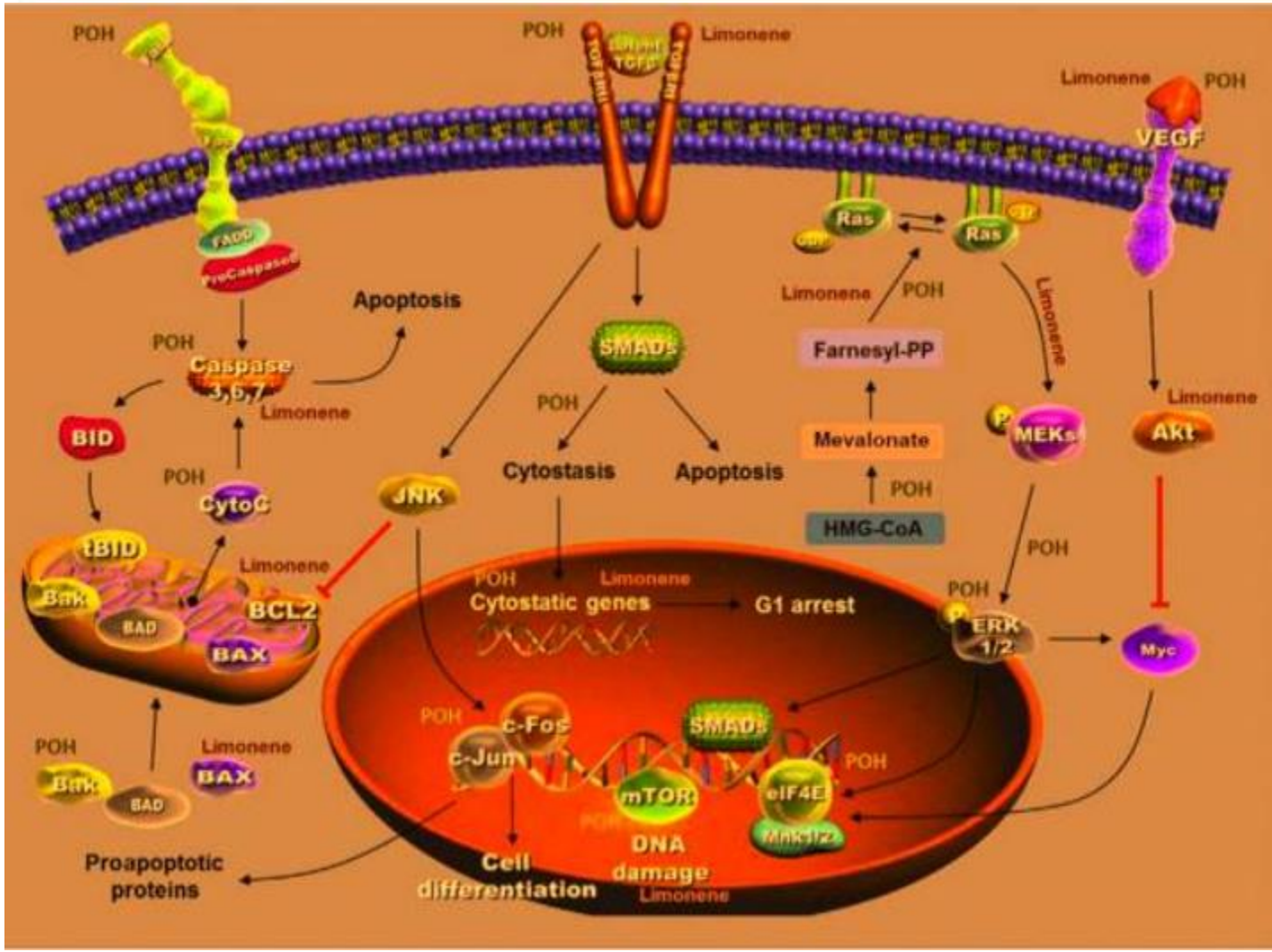


Vieira AJ, Beserra FP, Souza MC, et al. Limonene: Aroma of innovation in health and disease. Chem Biol Interact. 2018 Mar 1;283:97-106 PMID: 29427589

Limonene



- Anticancer
- Multiple patents on limonene-derived chemotherapy agents



Mukhtar YM, Adu-Frimpong M, Xu X, Yu J. Biochemical significance of limonene and its metabolites: future prospects for designing and developing highly potent anticancer drugs. Biosci Rep. 2018 Nov 13;38(6) PMID: 30287506

Peak Sugar Levels Much More Damaging than Average Blood Sugar

- Polyol and glycation activation greatly increased at higher glucose levels which results in the sequelae of diabetes
- MANY “Unimportant” plant constituents:
  - Decrease peak sugar
  - Inhibit polyol pathway
  - Inhibit glycation of proteins, enzymes, etc.

Hemoglobin A1c

- HbA1c is the standard, but:
- Not just average—the peaks are what cause the damage!
- However, misses daily fluctuations such as postprandial hyperglycemia, which can be detected with continuous glucose monitoring
- Patient 1 far more diabetes sequelae
-

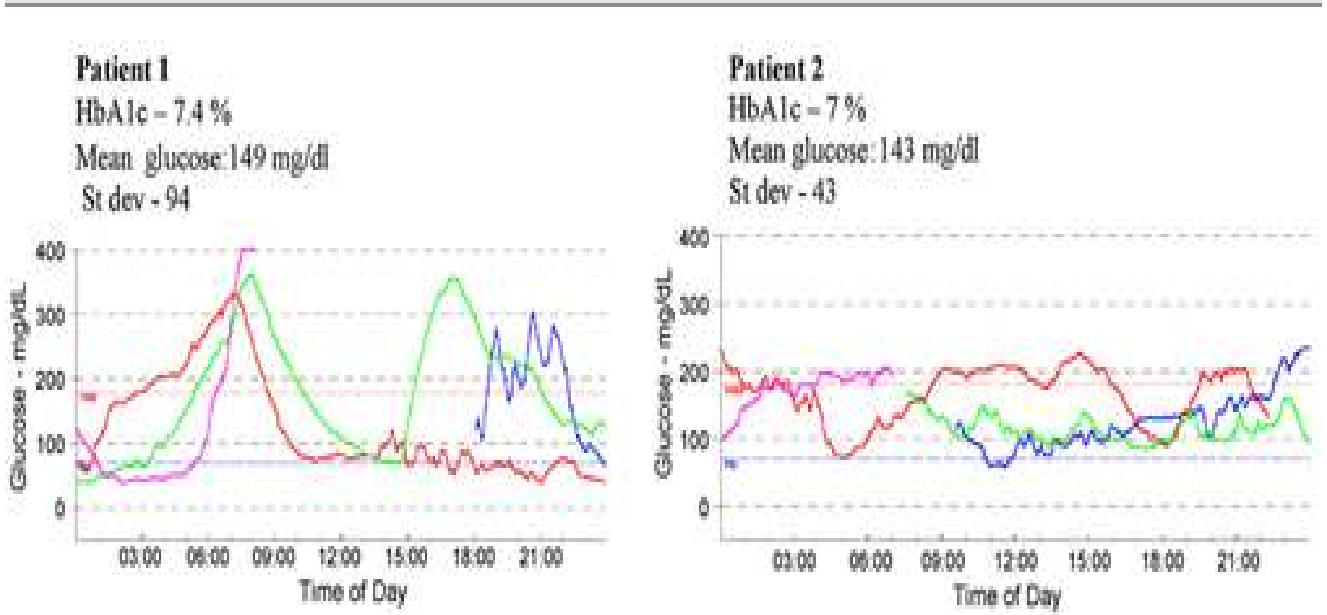
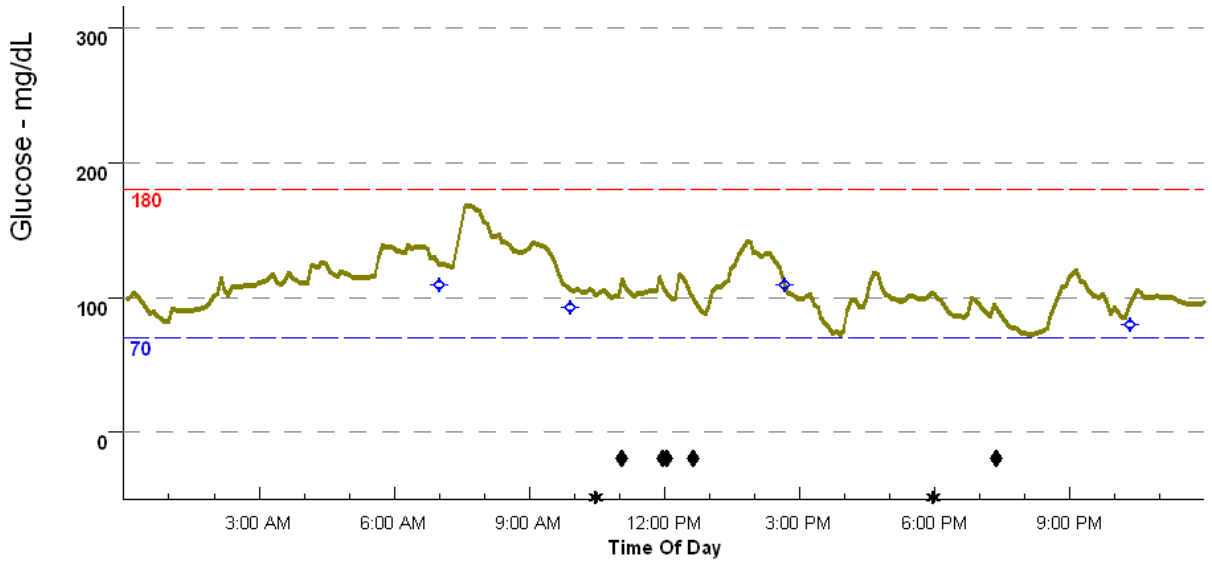


Fig. 1 – Continuous glucose monitoring of two patients at HbA1c target.

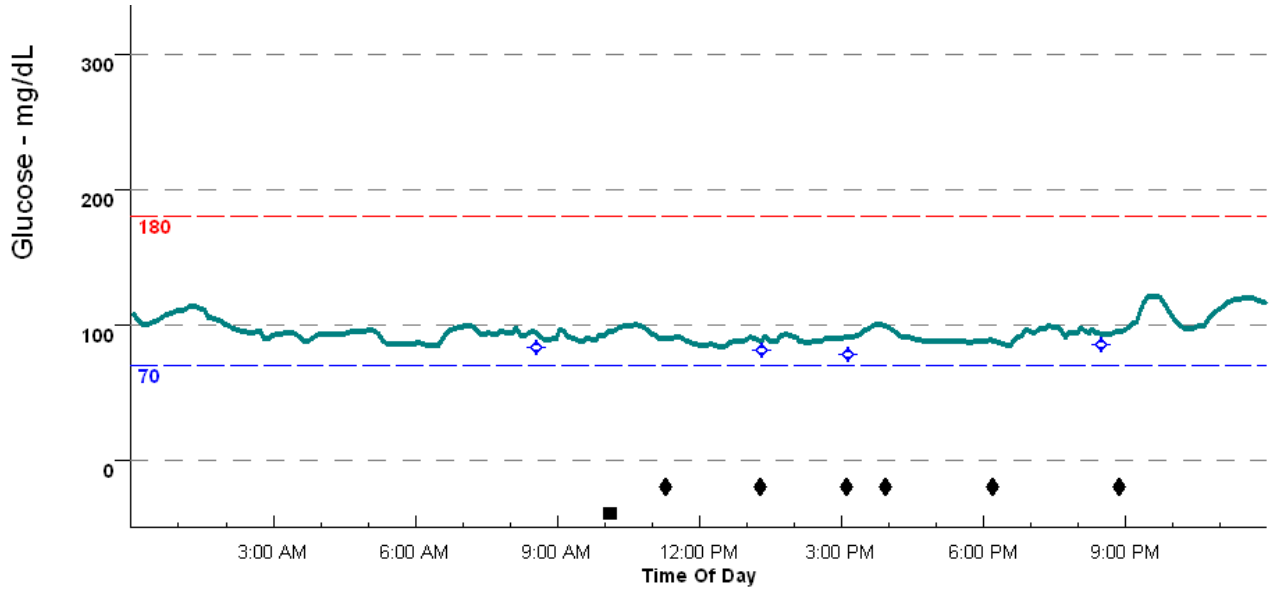
PMID: 19027978

Executive summary: standards of medical care in diabetes--2011. Diabetes Care. 2011 Jan;34 Suppl 1:S4-10
Hoeks LB, et al. Real-time continuous glucose monitoring system for treatment of diabetes: a systematic review. Diabet Med. 2011 Apr;28(4):386-94.

24-Hour Blood Sugar Monitor of Obese Diabetic



Standard diet

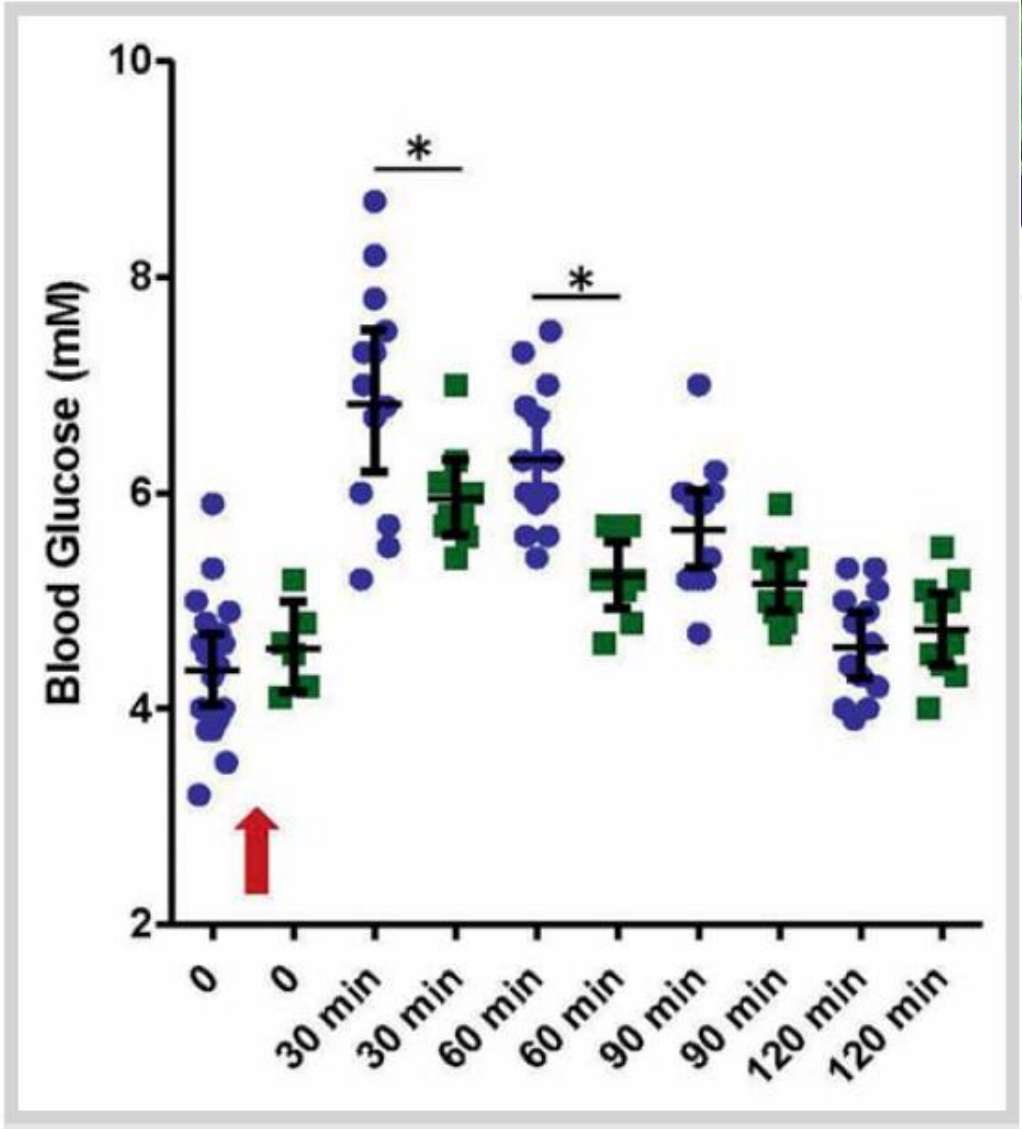


Standard diet + fiber

Personal communications Michael Lyon, MD

Chlorophyll

- Concept: Whole foods, plant-based diet has many constituents with unexpected health benefits
- Remember: glucose spikes cause the most damage



Blue dots: 75g glucose only
Green dots: Plus 1g chlorophyll

Gertsch J. The Metabolic Plant Feedback Hypothesis: How Plant Secondary Metabolites Nonspecifically Impact Human Health. Planta Med. 2016 Jul;82(11-12):920-9 PMID: 27286339

Theme 6

ORGANICALLY-GROWN FOODS MORE HEALTHFUL THAN CHEMICALLY-GROWN FOODS

Just the Tip of the Iceberg

Parameters	Food produce	Organic versus conventional	References
Vitamins: e.g., vitamin C, vitamin E, and carotenoids	Fruit, vegetables	Higher (most studies)	7, 11, 17, 49, 115
Minerals: calcium, potassium, phosphorous, magnesium, iron	Fruit, vegetables, cereals	Higher	11, 14, 28, 49, 93, 99, 118
Nitrate	Fruit, vegetables, cereals	Lower	7, 17, 61, 69, 115, 118
Antioxidant activity	Fruit, vegetables, cereals	Higher	7, 11, 17, 49, 61, 93
Phenolic compounds (total)	Fruit, vegetables, cereals	Higher	7, 18, 99
Protein, amino acids, nitrogen	Fruit, vegetables, cereals	Lower	7, 28
Beneficial fatty acids, i.e., eicosapentaenoic acid, docosapentaenoic acid, docosahexaenoic acid, α-linolenic acid, and conjugated linoleic acid	Milk, meat	Higher	61, 87, 102, 103
Iodine and selenium	Milk	Lower	102, 103
Cadmium	Fruit, vegetables, cereals	Lower in cereals	7
Pesticide residues	Fruits, vegetables, and grains	Lower risk for contamination	6, 14, 61, 69, 99
Fusarium toxins	Cereals	Similar or lower in organic	99
Microorganisms, antibiotic-resistant bacteria	Chicken and pork		99

Brantsæter AL, Ydersbond TA, Hoppin JA, et al. Organic Food in the Diet: Exposure and Health Implications. Annu Rev Public Health. 2017 Mar 20;38:295-313 PMID: 27992727

Huge Clinical Impact

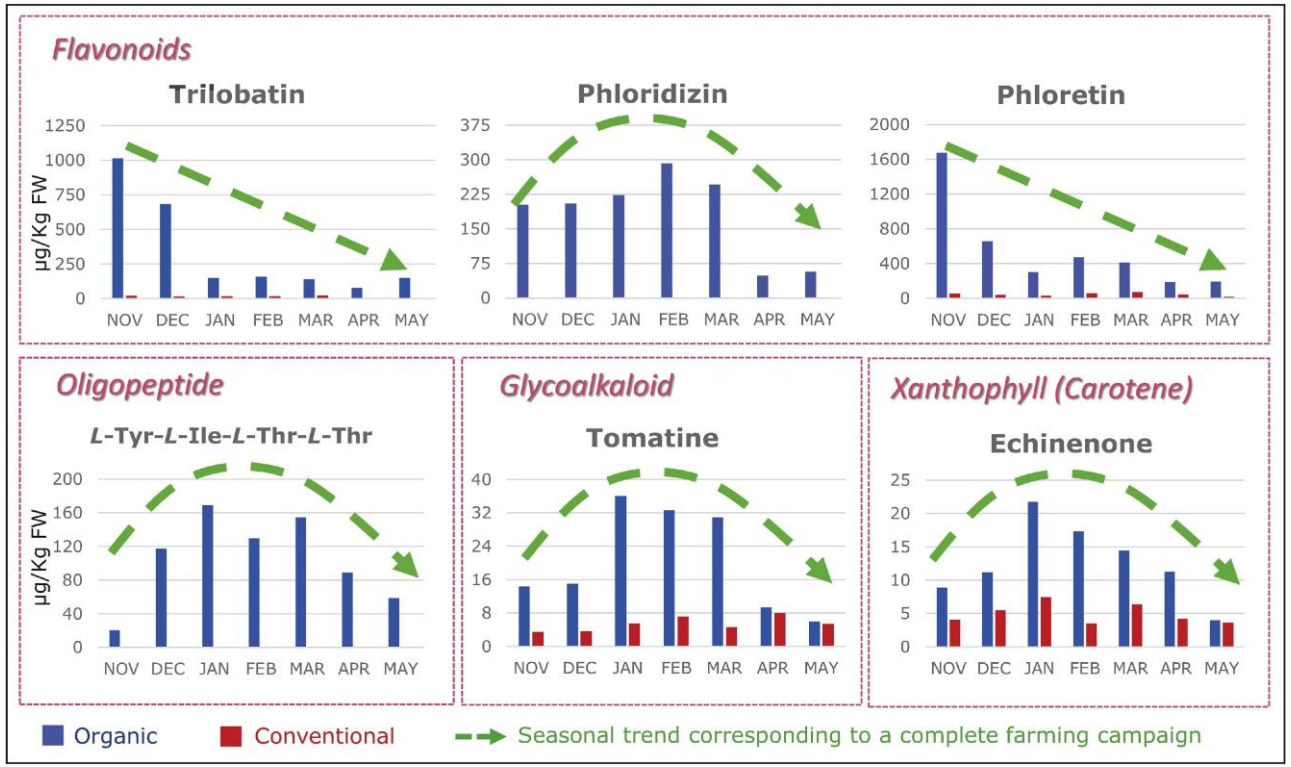
End point	Study population and design	Exposure	Result	References
Atopy	Cross-sectional study in 295 children from families with anthroposophic lifestyle and 380 children from control families in Sweden	Organic food consumption as part of an anthroposophic lifestyle	Less atopy in the children coming from anthroposophic families	4
Allergies and atopic sensitization	Cross-sectional study including 14,893 children aged 5–13 years from anthroposophic families and reference children from five European countries (Austria, Germany, the Netherlands, Sweden, and Switzerland)	Organic food consumption as part of an anthroposophic lifestyle	Fewer allergies in families with anthroposophic lifestyle	3
Hay fever and asthma-like symptoms	Cross-sectional study in 593 organic and 1,205 conventional farmers in the Netherlands	Organic versus conventional farming practice	No difference in respiratory disease associated with farming practice/organic consumption	98
Eczema and/or wheeze occurrence	Prospective follow-up of 2,700 children in the KOALA birth cohort in the Netherlands. Blood samples from 815 infants at 2 years of age were analyzed for total and specific immunoglobulin-E	Organic consumption in six food groups and proportion of organic within the total diet	No difference in atopic sensitization. Less eczema with consumption of organic dairy products but not with other organic foods or proportion of organic food	60
Allergic sensitization	Prospective study of 330 children from families with anthroposophic, partly anthroposophic, or nonanthroposophic lifestyle in Sweden. Allergen-specific immunoglobulin-E sensitization measured in blood	Organic food consumption as part of an anthroposophic lifestyle	Immunoglobulin-E sensitization to common allergens was lower among children of families with an anthroposophic lifestyle	104
Hypospadias	Case-control study in mothers of 306 boys who were operated on for hypospadias and 306 mothers of healthy boys	Retrospective recall of organic consumption in six food groups during pregnancy	No difference with any organic consumption but higher prevalence with nonorganic milk/dairy combined with frequent consumption of high fat dairy products	23
Hypospadias and cryptorchidism	Prospective study in 35,107 mothers of singleton male infants in Norway 2002–2008	Organic food in six food groups assessed by FFQ grouped into frequent versus sometimes	Lower prevalence of hypospadias with any organic consumption, and in particular organic vegetables. No difference for cryptorchidism	19
Preeclampsia	Prospective study in 28,192 first time singleton pregnant mothers in Norway 2002–2008	Organic food in six food groups assessed by FFQ grouped into any versus seldom/never	Lower prevalence of preeclampsia with frequent organic vegetables, no difference for other food groups or any organic consumption	106
Sperm quality	Cross-sectional study in 30 members of organic farming organizations and 73 blue-collar workers as controls in Denmark in 1994	Organic farmers had a high proportion of organic food in their diets	Higher sperm density in organic farmers	1
Sperm quality	Cross-sectional study in 55 members of organic farming organizations (age 20–45 years) and 141 controls working in an airline company (age 23–43 years) in Denmark in 1996	The organic farmers had at least 25% organic food in their diets	Higher sperm quality in organic food consumers	54
Sperm quality	Cross-sectional study in 85 organic (mean age 40 years) and 171 conventional farmers (mean age 38 years) in Denmark in 1995/1996	Organic food consumption assessed by FFQ and grouped into 0%, 1–49%, and 50–100% organic fruits and vegetables	Lower concentration of morphologically normal spermatozoa in the group with no organic food intake. No differences in 14 other parameters	57
Sperm quality	Cross-sectional study in 85 organic (mean age 40 years) and 171 conventional farmers (mean age 38 years) in Denmark in 1995/1996	Comparison of pesticide exposure and sperm quality between organic and conventional farmers	No difference in sperm quality between organic and conventional farmers	62
Cancer incidence, overall and for 17 individual cancer sites	Prospective study in 623,080 British women with follow-up for 9.3 years from 2002 to 2011	Organic consumption (any food group) in four categories; never, sometimes, usually, or always	No differences for all cancer incidence between usually/always versus never organic	15
Risk factors for cardiovascular disease	Intervention study, crossover design with 150 Italian men (100 healthy and 50 patients with chronic liver disease) in 2006–2008. Outcomes: BMI by dexa scan and blood parameters	Two weeks intervention with Mediterranean conventional diet (T1) and Mediterranean organic diet (T2)	Significant reduction in risk factors for cardiovascular disease after the T2 period	30

Abbreviations: BMI, body-mass index; FFQ, Food Frequency Questionnaire; KOALA, Kind, Ouders en gezondheid: Aandacht voor Leefstijl en Aanleg (Child, parents and health, addressing lifestyle and constitution).

Brantsæter AL, Ydersbond TA, Hoppin JA, et al. Organic Food in the Diet: Exposure and Health Implications. Annu Rev Public Health. 2017 Mar 20;38:295-313 PMID: 27992727

Dramatic Difference Between Organic- and Chemically-Grown Foods

- Tomatoes
- Highly controlled greenhouse
- Shows variation over normal growth cycle
- Dramatic decrease in “unimportant” molecules
- Note: the coloring molecule echinenone (beta-carotene variant) is least reduced



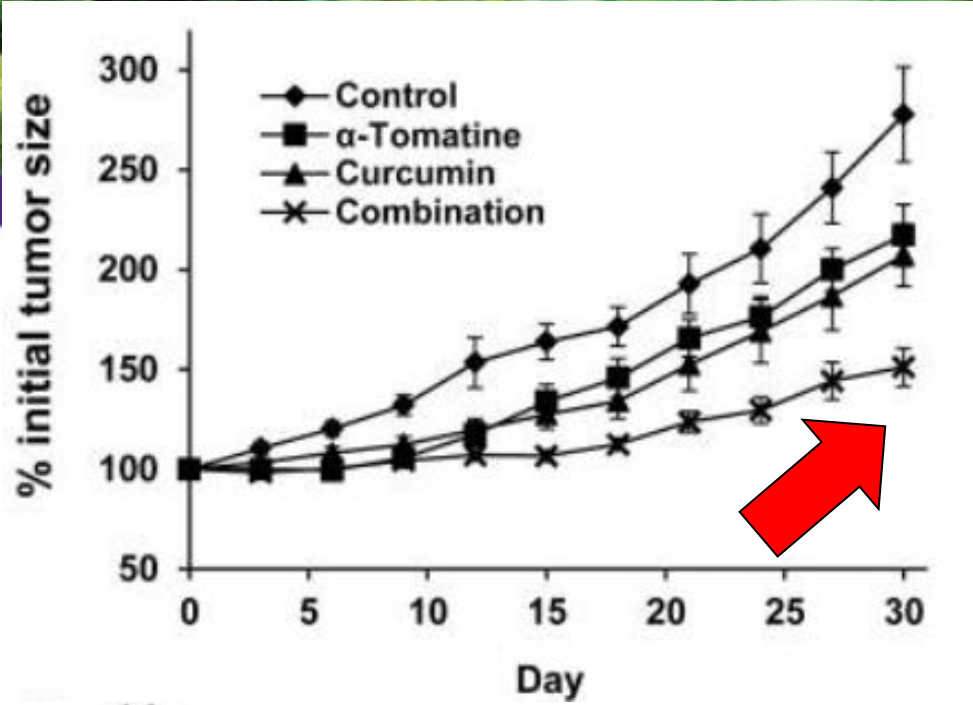
Martínez Bueno MJ, Díaz-Galiano FJ, Rajski Ł, et al. A non-targeted metabolomic approach to identify food markers to support discrimination between organic and conventional tomato crops. J Chromatogr A. 2018 Apr 20;1546:66-76 PMID: 29526497

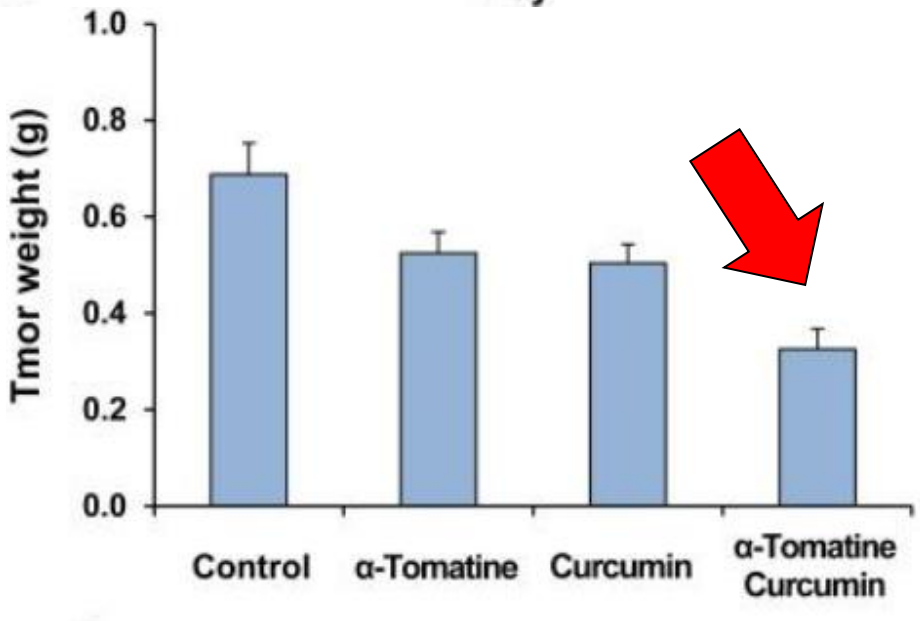
Tomatine

- The major saponin in tomatoes

- Antitumor, antioxidant, anti-inflammatory
- Suppresses production of pro-inflammatory cytokines in lipopolysaccharide (LPS)-induced macrophages
- Human prostate cancer cells

Note synergistic effects

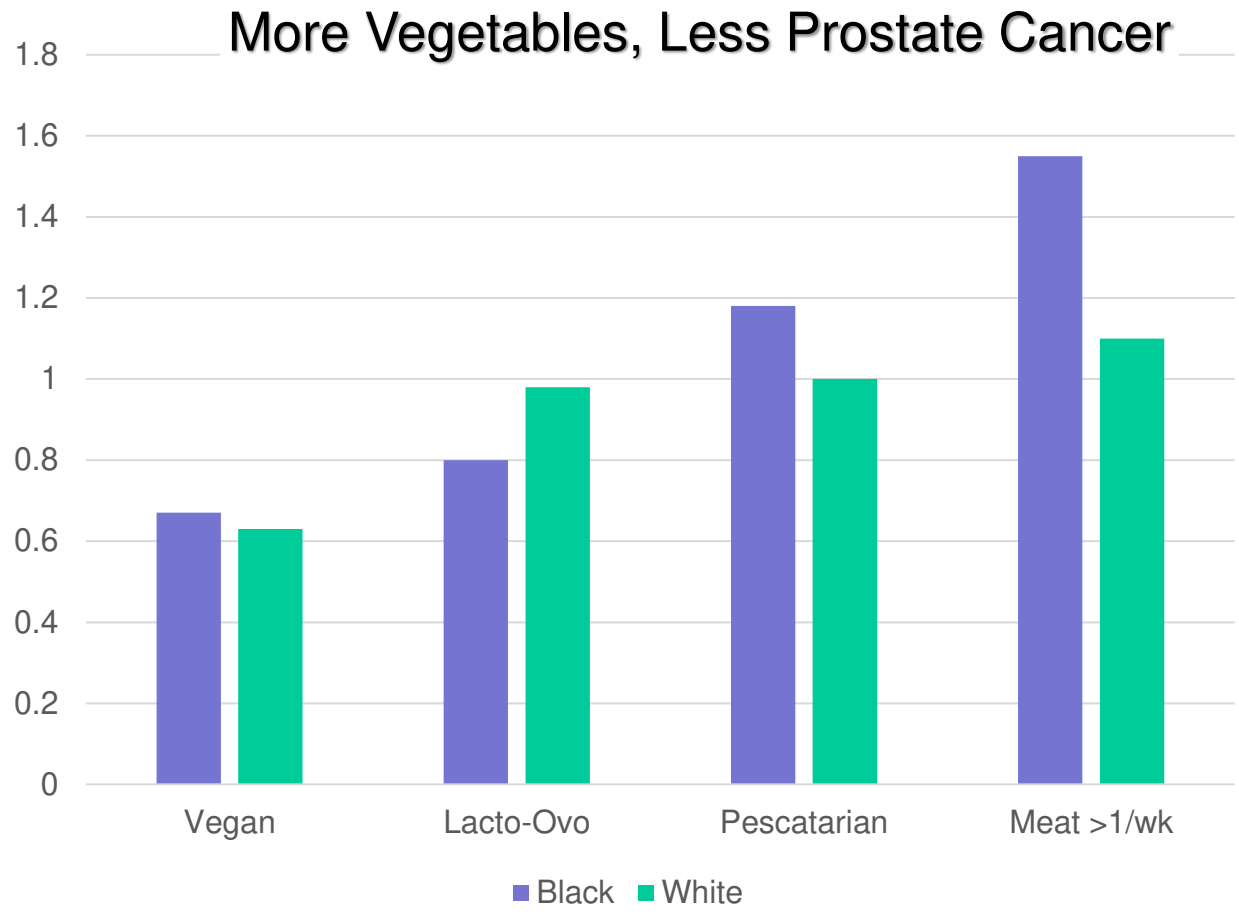




Huang H, Chen X, Li D, et al. Combination of α-Tomatine and Curcumin Inhibits Growth and Induces Apoptosis in Human Prostate Cancer Cells. PLoS One. 2015 Dec 2;10(12) PMID: 26630272

Tomatine, etc. Clinically Significant

- Virtually no direct clinical research on tomatine in humans
- Implied research comparing vegans to other eating patterns
- Research inconsistent ranging from no statistical difference to substantial protection
- Probable cause is uncontrolled variance in genomics of test populations and quality of food



Tantamango-Bartley Y, Knutsen SF, Knutsen R, et al. Are strict vegetarians protected against prostate cancer? Am J Clin Nutr. 2016 Jan;103:153-60

The “Unimportant” Molecules Greatly Impact “Important” Nutrients

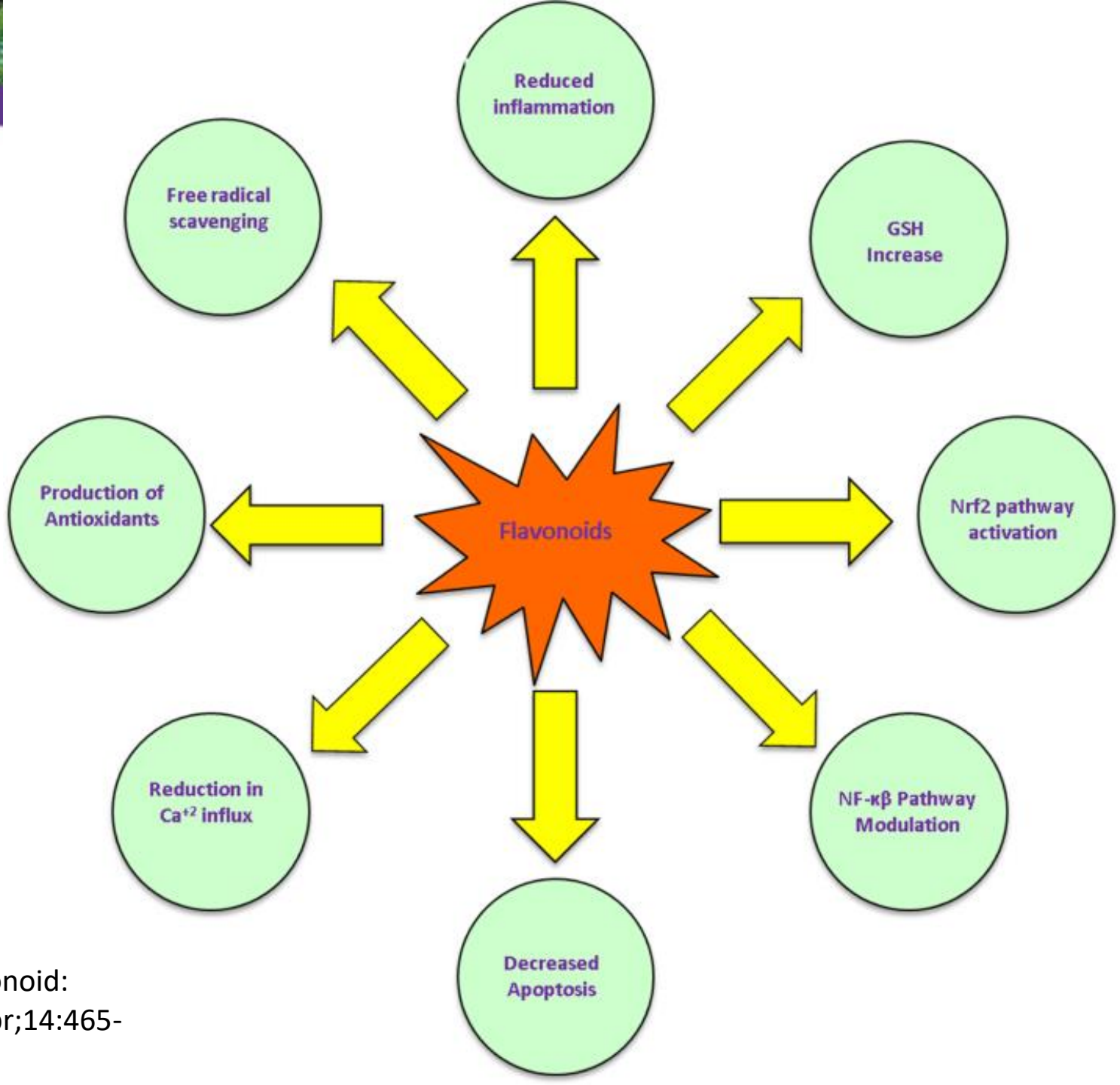
- Zinc critical for metabolism—**but only if in cells**
- Bioflavonoids increase zinc transport into cells
- Foods depleted in zinc and also depleted in bioflavonoids have even lower cellular zinc
- Foods grown with high phosphates typically have higher levels of zinc-antagonist cadmium

Favonoids Critical to Transport of Zinc Into Cells

- Cell study
- Dietary plant polyphenols such as flavonoids quercetin and epigallocatechin-gallate are zinc ionophores
  - Transport zinc cations through the plasma membrane
- Numerous enzymes dependent on zinc are activated by polyphenols
- Combination of zinc and flavonoids dramatically increase zinc levels in cells and metabolic activity of Zn-dependent enzymes

Dabbagh-Bazarbachi H, Clergeaud G, Quesada IM, et al. Zinc ionophore activity of quercetin and epigallocatechin-gallate: from Hepa 1-6 cells to a liposome model. J Agric Food Chem. 2014 Aug 13;62(32):8085-93 PMID: 25050823

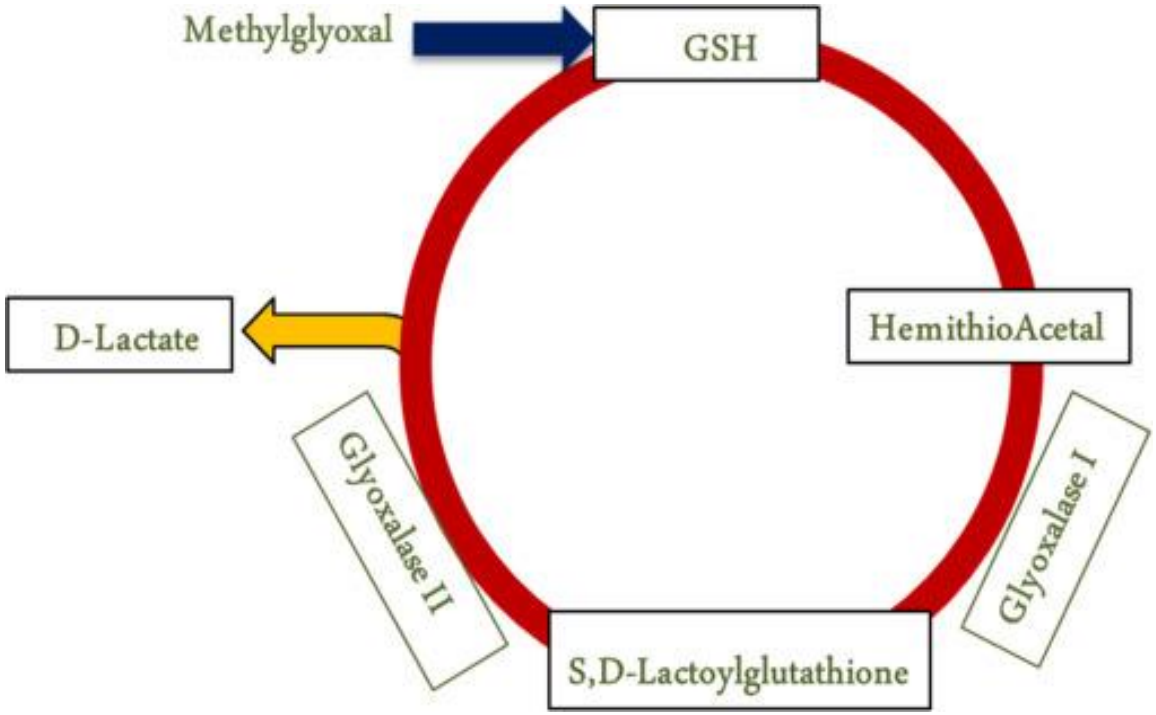
Flavonoids Critical For Health



Frandsen JR, Narayanasamy P. Neuroprotection through flavonoid: Enhancement of the glyoxalase pathway. Redox Biol. 2018 Apr;14:465-473 PMID: 29080525

Preserving Our Brains

- Flavonoids enhance glyoxalase pathway
- Detoxifies reactive dicarbonyl compounds, esp. methylglyoxal
- Critical antioxidant neuron protection
- Decreases risk for:
  - Alzheimer's
  - Parkinson's
  - Aging
  - Autism Spectrum Disorder



Frandsen JR, Narayanasamy P. Neuroprotection through flavonoid: Enhancement of the glyoxalase pathway. Redox Biol. 2018 Apr;14:465-473
PMID: 29080525

The Higher Level of "Unimportant" Molecules in Organically-Grown Foods Has Huge Clinical Implications

- Lower risk of cancer: OR 0.75 (0.23 for lymphomas!)
- Not just lower pesticide levels

Baudry J, Assmann KE, Touvier M, et al. Association of Frequency of Organic Food Consumption With Cancer Risk: Findings From the NutriNet-Santé Prospective Cohort Study. JAMA Intern Med. 2018 Dec 1;178(12):1597-1606 PMID: 30422212

Why Do Organic Foods Taste Better?

- Three strawberry cultivars grown both chemically and organically
- 79% variation in metabolome explained 88% of variation in sensory profiles
- Sensory variations due to flavonoids, tannins and fatty acids
- Organic farming practices enhance accumulation of sensory plant metabolites

⇒ Full taste, not overstimulation of 1 or 2 sensors = health

Kårlund A, Hanhineva K, Lehtonen M, et al. Nontargeted metabolite profiles and sensory properties of strawberry cultivars grown both organically and conventionally. J Agric Food Chem. 2015 Jan 28;63(3):1010-9 PMID: 25569122

Many Studies Show Organic Foods Higher in Nutrients

- Onions: phenolics, total flavonoids and antioxidant activity
- Broccoli: indolyl glucosinolates (precursors of I3C)

Ren F, Reilly K, Gaffney M, et al. Evaluation of polyphenolic content and antioxidant activity in two onion varieties grown under organic and conventional production systems. J Sci Food Agric. 2017 Jul;97(9):2982-2990 PMID: 27859352
Valverde J, Reilly K, Villacreces S, et al. Variation in bioactive content in broccoli (Brassica oleracea var. italica) grown under conventional and organic production systems. J Sci Food Agric. 2015 Apr;95(6):1163-71 PMID: 24976520

Why Disconnect Between Nutrient Levels and Metabolites?

- Blood levels of nutrients poorly predict metabolite levels
- Why?
  - Methylation polymorphisms only partial explanation
  - Virtually all B12 measurements do not differentiate between cyano-cobalamin, methyl-cobalamin and adenosyl-cobalamin
  - Rarely measure holo-cobalamin—the key transport molecule into cells

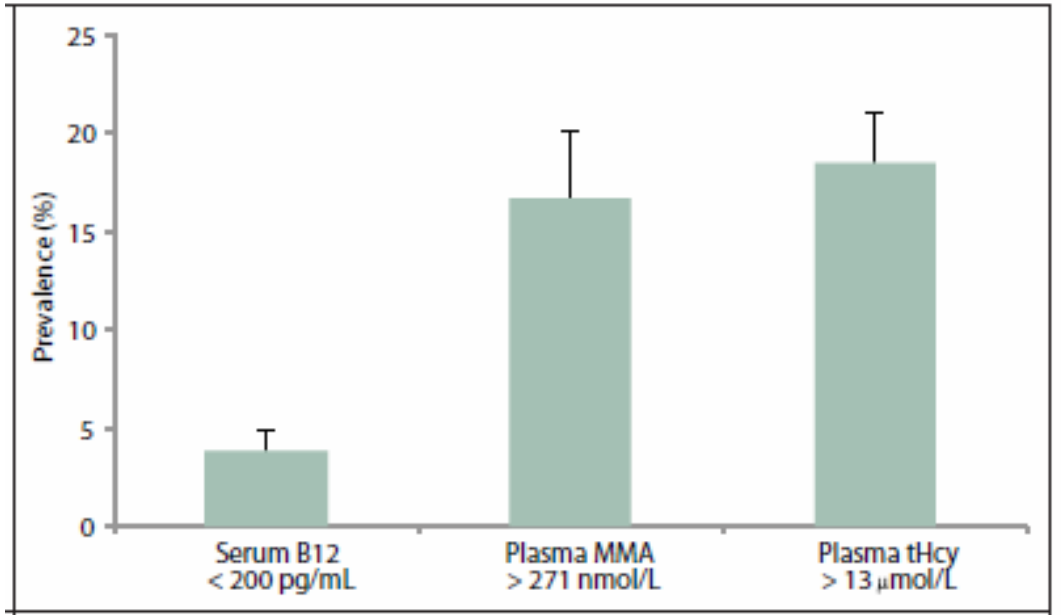


Figure H.1.d. *Prevalence estimates of low serum vitamin B12 (B12), high plasma methylmalonic acid (MMA), and high plasma total homocysteine (tHcy) concentrations in U.S. persons 60 years and older, National Health and Nutrition Examination Survey, 2003–2006.*

Data shown for plasma MMA are from NHANES 2003–2004 only. Error bars represent 95% confidence intervals.

CDC. Second National Report on Biochemical Indicators of Diet and Nutrition in the U.S. Population (2012). Page 20

Theme 7

LOSS OF SYNCHRONIZATION WITH ENVIRONMENT

Circadian Rhythms and Epigenetics Highly Impacted by Environment

- The Circadian Clock is an endogenous timekeeping system that synchronizes physiology and behavior to day/night cycles
- Circadian clocks exist in nearly every cell, tissue, and organ system
- Virtually every cell has sensors sampling environmental signals

Partch, C.L., Green, C.B., & Takahashi, J.S. (2014). Molecular architecture of the mammalian circadian clock. Trends in Cellular Biology, 24(2), 90-9. PubMed PMID: 23916625.
Yamazaki, S., Numano, R., Abe, M., Hida, A., Takahashi, R., Ueda, M., Block, G.D., Sakaki, Y., Menaker, M., & Tei, H. (2000). Resetting central and peripheral circadian oscillators in transgenic rats. Science, 288(5466), 682-5. PubMed PMID: 10784453.

Aryl Hydrocarbon Receptor (AhR)

- Ligand-activated transcription factor that regulates gene expression
- Originally considered a sensor of xenobiotic chemicals and as the regulator of the cytochrome P450s that metabolize these toxic chemicals.
- Now known to:
  - Respond to many endogenous and exogenous molecules
  - Plays a major role in circadian clockwork

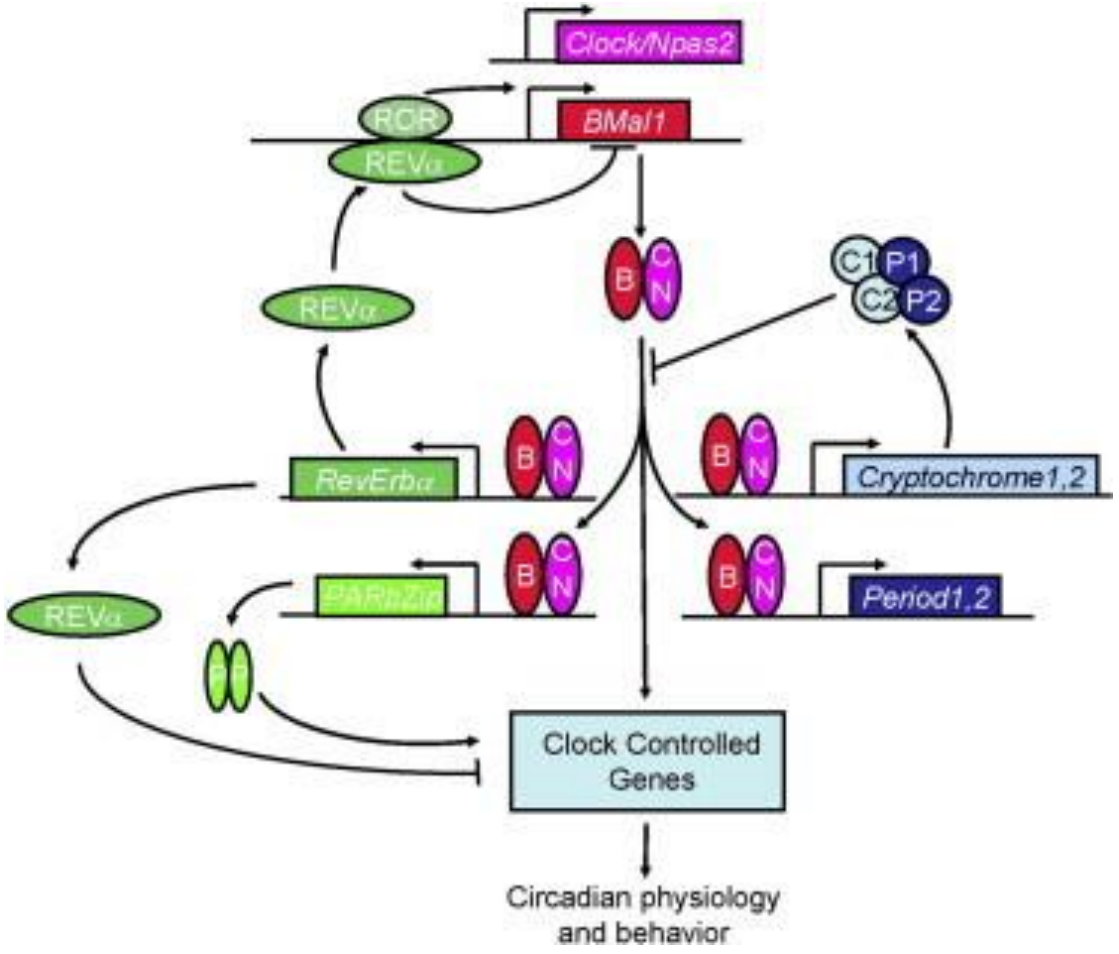
Anderson, G., Beischlag, T.V., Vinciguerra, M., & Mazzoccoli, G. (2013). The circadian clock circuitry and the AHR signaling pathway in physiology and pathology. Biochemical Pharmacology, 85(10), 1405-16. PubMed PMID: 23438471.

AhR Ligands

Endogenous Ligands	Natural Compounds	Exogenous Ligands
Indigoids	Flavonoids	Halogenated dioxins
Equilenin	Carotenoids	Polychlorinated biphenyls
Arachidonic acid metabolites	Berberine	Polycyclic aromatic hydrocarbons
Heme metabolites		Pesticides
Tryptophan metabolites		

Garrett, R.W., & Gasiewicz, T.A. (2006). The aryl hydrocarbon receptor agonist 2,3,7,8-tetrachlorodibenzo-p-dioxin alters the circadian rhythms, quiescence, and expression of clock genes in murine hematopoietic stem and progenitor cells. Molecular Pharmacology, 69(6), 2076-2083.

Toxins Impact Circadian Gene Expression



Circadian gene	Toxin	Receptor
BMal1	WY14643	PPARα
	TCDD	AhR
Per1	FICZ	AhR
	TCDD	AhR
Per2	TCDD	AhR
Per3	DEHP	PPARα
Cry1	FICZ	AhR
	DEHP	PPARα
Cry2	FICZ	AhR
Dbp	DEHP	PPARα

Claudel, T., Cretenet, G., Saumet, A., & Gachon, F. (2007). Crosstalk between xenobiotics metabolism and circadian clock. FEBS Letters, 581(19), 3626-33. PubMed PMID: 17451689

DEHP (Bis(2-ethylhexyl) phthalate)
DHEP (Di(2-Ethylhexyl) phthalate)

- Used to soften PVC plastic products such as:
  - Wall coverings, tablecloths, floor tiles, furniture upholstery, shower curtains, garden hoses, swimming pool liners, rainwear, baby pants, dolls, some toys, shoes, automobile upholstery and tops
  - Food packaging films
  - Sheathing for wire and cable
  - Medical tubing and blood storage bags
- Contaminant in many water supplies

⇒ **DHEP/DEHP constantly disrupt Circadian Rhythm and dis-integrates epigenetics from environment**

PUTTING IT ALL TOGETHER

WE'VE MOVED FROM LIVING IN A MATRIX OF HEALTH-PROMOTING MOLECULES IN SYNCHRONY WITH THE ENVIRONMENT

to

A MIASMA OF TOXINS, DEFICIENCIES AND ISOLATION RESULTING IN HIGH DISEASE BURDEN

CONVERTING DISEASE RISK TO % OF DISEASE DUE TO TOXINS

Converting Disease Risk to % Caused: Attributable Fraction (AF) Calculation

$$AF = \frac{p(rr-1)}{p(rr-1)+1}$$

p = underlying prevalence of risk factor in the population

rr = relative risk (risk of contracting a disease in an exposed population divided by the risk of contracting the disease in an unexposed population)

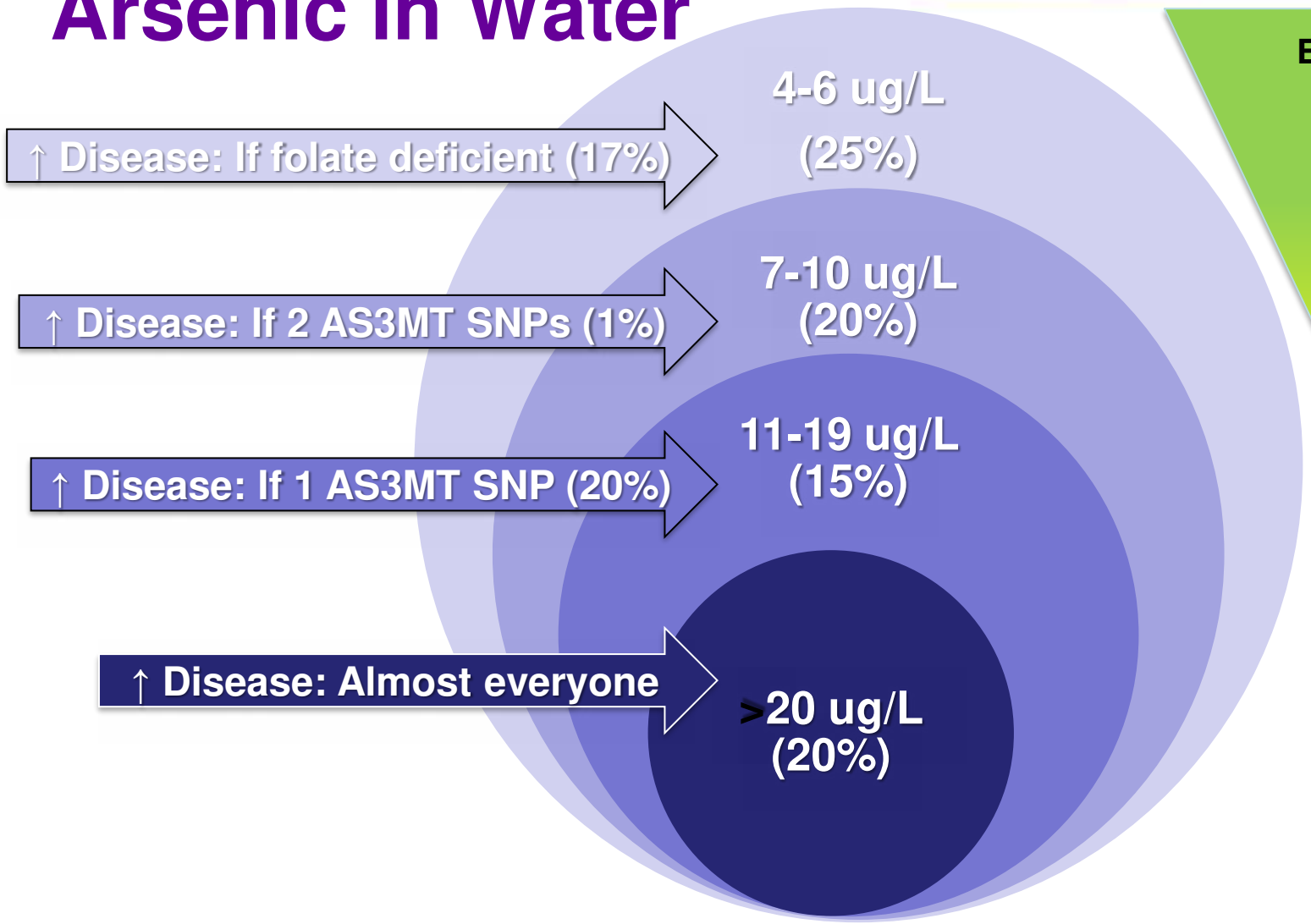
AF = % of disease due to the toxin

Levin, M. The occurrence of lung cancer in man. *Acta Unio Int. Contra Cancrum*. 1953, 9, 531-541

Arsenic and Disease

Disease	Threshold	% Above Threshold	Odds Ratio	% of Disease	Example PMID
Gout	12.5 ug/L	25%	5.5	52%	25499256
Cancer, prostate	13.3 ug/g	20%	3.3	32%	23800676
Cancer, pancreatic	13.3 ug/g	20%	2.5	23%	23800676
Diabetes	16.5 ug/L	20%	2.1	18%	18714061
Cancer, bladder	10.0 ug/L	10%	2.7	14%	24889821

Arsenic in Water



(Prevalence from research; thresholds only estimated at this time; water estimated from urine)

Naturopathic Therapeutic Order

Establish Foundations for Optimal Health
Remove Obstacles to Cure

Stimulate self-healing mechanisms
Recognize the Vis Medicatrix Naturae

Restore Weakened Systems
Aid in Regenerations of Damaged Organs

Restore Structural Integrity
Address Physical Alignment

Natural Symptom Control
Natural Substances to Palliate

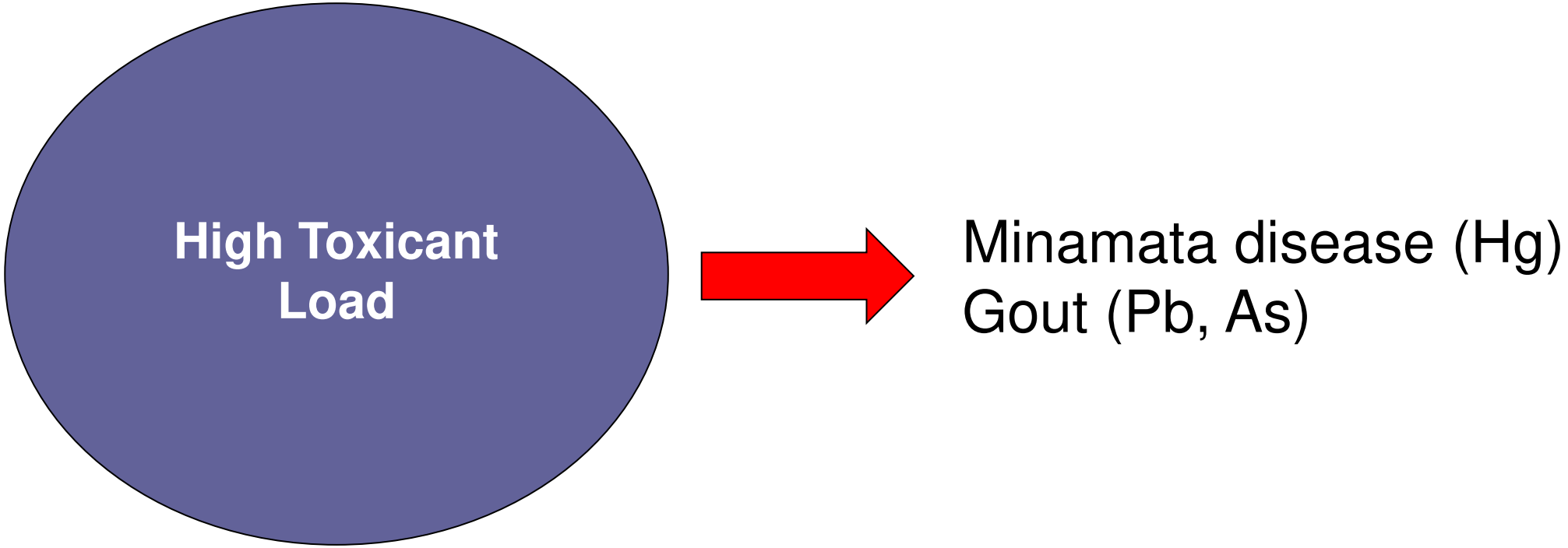
Synthetic symptom relief
Pharmaceuticals to Palliate

High force intervention
Suppress Pathology

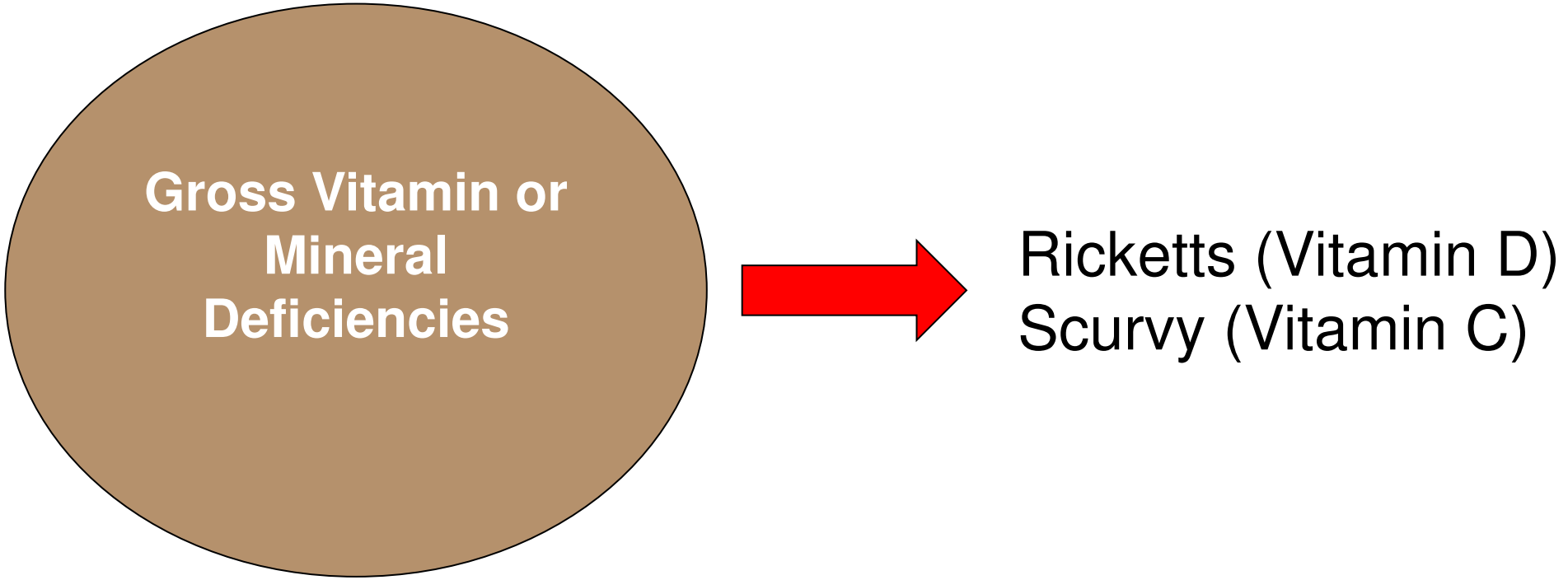
Clinical Application

1. Arsenic in water >20.0 ug/L is toxic for everyone
   (2% of reported US public water supplies, higher in private wells)
2. Arsenic in water >10.0 ug/L is toxic for everyone, if also another exposure such as regularly eating chicken or rice
   (10% of **reported** US public water supplies, higher in private wells)
3. If 1 of 2 AS3MT SNPs, toxic effects >11.0 ug/L of water or significant other arsenic sources (regularly eating rice or chicken)
   - Incidence of SNPs 8% and 14% ⇒ 21% experience toxicity at “safe” levels
4. If both AS3MT SNPs, toxic effects >7.0 ug/L or significant other arsenic exposures
   - 1% likely to suffer arsenic toxicity if regularly eating rice and chicken, even if water arsenic not high. Deadly if also As in water.
5. B-vitamin supplementation if homocysteine > 8.0
6. Glutathione support (NAC: 500 bg bid)
7. Treat water if above 5.0 ug/L

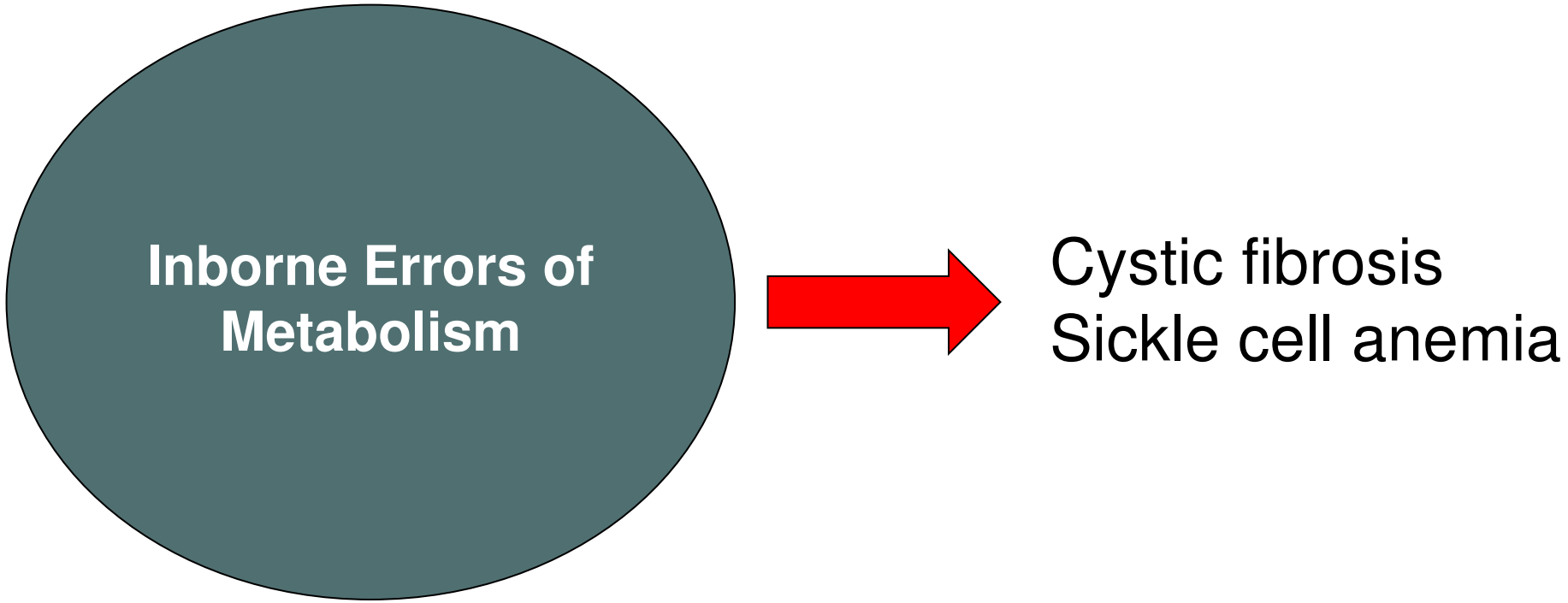
High Toxicant Load Causes Disease



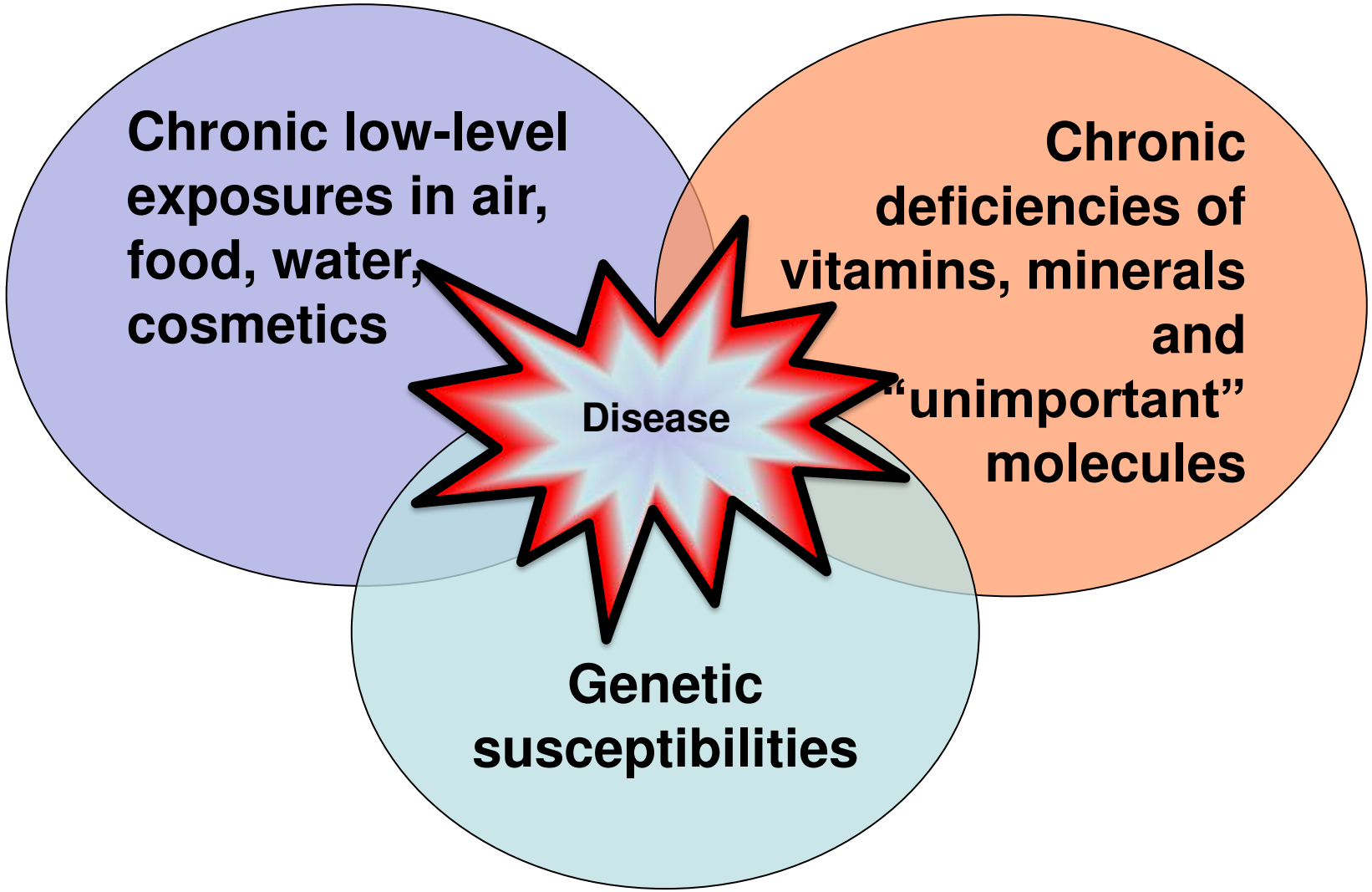
Gross Nutritional Deficiencies Cause Disease



Some Diseases Really Are Caused by Genetics



Unified Theory of Disease



Any Wonder Why Chronic Disease is Epidemic?

- We transformed the food supply to be deficient not just in nutrients known to be required for metabolism but also “unimportant” molecules that hugely impact health

- Then we create drugs that are patentable modifications of some of these “unimportant” molecules and prescribe them to the population for the diseases caused by a depleted food supply.

- Now add toxins and toxicants to further poison metabolism…

Bottom Line

- There is no substitute for a whole foods diet
  - Primarily plant based
  - Organically grown
  - Heirloom seeds
  - Uncontaminated during growing, transport, processing, storage and cooking
- Nutritional supplements are not a substitute for a whole foods diet
  - Most valid use of supplements are for addressing genomic susceptibilities, protecting from toxic world, enhancing function when needed (e.g. antiaging)

Substituting drugs for natural food molecules will never be an effective strategy

Mom Was Right! Eat your vegetables!

Eat your organically grown, heirloom vegetables!

BENEFICIAL

EXPOSOME