Integrative Healthcare SYMPOSIUM

Environmental Toxins & Autoimmune Disease

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Disclosures

- I have no disclosures.

Objectives

- **Discuss** the plethora of toxics in the human environment
- **Discuss** the epidemiology of autoimmune disease
- **Discuss** cellular mechanisms for a variety of toxics on immune system function
- **Explain** both conventional and integrative/functional approaches to reducing toxic exposures
- **Apply** evidence-based strategies for patient management of autoimmune disorders

In


Poland Spring
NATURAL SPRING WATER
SPARKLING


Yoplait
light
strawberry
flavored with other natural flavor


talenti
GELATO
Mediterranean Mint
ONE PINT (473ML)


MORNINGS MADE SIMPLE
nutella
FERRERO
Hazelnut Spread with Cocoa


JIF
EXTRA CRUNCHY
PEANUT BUTTER
NET WT 16 OZ (1 LB) 454g


RUBY RED GRAPEFRUIT
Florida's Natural
100%
PREMIUM RUBY RED GRAPEFRUIT JUICE


La Vieille
Three Thieves
CABERNET SAUVIGNON


CAPE COD
Kettle Cooked
Potato Chips
% Reduced Fat*
Original
NON GMO Project
VERIFIED


strawberry ARTIFICIAL FLAVOR
JELL-O
NO artificial sweeteners
NO high fructose corn syrup
same great taste
NET WT 6 OZ (170g)


NUTRITIONAL SUPPORT FOR
6 KEY VITAL FUNCTIONS*
IMPROVED FORMULA:
NO Artificial Colors
ONE A DAY
WOMEN'S
Complete Multivitamin
MULTIVITAMIN/MULTIMINERAL SUPPLEMENT
100 TABLETS


NO SUGAR NO CALORIES
Diet
Coke


Breyers
100% GRADE A
milk and cream
Homemade Vanilla
It's How Homemade Should Taste


since 1842
MOTT'S
Applesauce

On


ANTISEPTIC
LISTERINE
COOL MINT
FOR A FRESHER & CLEANER MOUTH THAN BRUSHING ALONE
ADA Accepted


INVISIBLESOLID
Secret
pH balanced
powder fresh


TAMPAX
multipax
16 super


BANANA BOAT
KIDS
SPORT
50
POWERSTAY
TECHNOLOGY
Tear+sting free


Colgate
Total
DEEP CLEAN


BRONZING
MAC
POWDER


50% more
BONUS
Purell


Gillette
Foamy
REGULAR
ORIGINALE
CAUTION/ATTENTION


O·P·I
NAIL LACQUER


NEW
SMOOTHER GLIDE
AXE
APOLLO
48H
DRY


PANTENE
PRO-V
RADIANT
COLOR
SHINE
SHAMPOO


NIVEA
IN-SHOWER
BODY LOTION
24hr+
NOURISHING


CVS
pharmacy
non-acetone
polish
remover


BAUSCH+LOMB
Bio
true

Around


MULTI-SURFACE CLEANER
ORIGINAL
Pine-Sol
KILLS 99.9% OF GERMS


method
ALL-PURPOSE
naturally derived
surface cleaner
pink grapefruit
pamplemousse rose


50
Country Comfort
PUMPKIN SPICE
SCENTED
CANDLE


HARDWORKING HOMEKEEP
Mrs. MEYER'S
CLEAN DA
AROMATHERAPEUTIC HOUSEHOLD
LAVENDER
SCENT


80 OZ
VALUE SIZE
GREAT ON TOUGH
HAIR CLOGS
GUARANTEED!
OR IT'S FREE*
PRO
STRENGTH
Drano
MAX GEL


Long-Lasting Fragrance
CLOROX
LAVENDER
SPLASH-LESS


pledge
Furniture
Spray
ORANGE
CLEAN
For a noticeable clean
on wood and more!

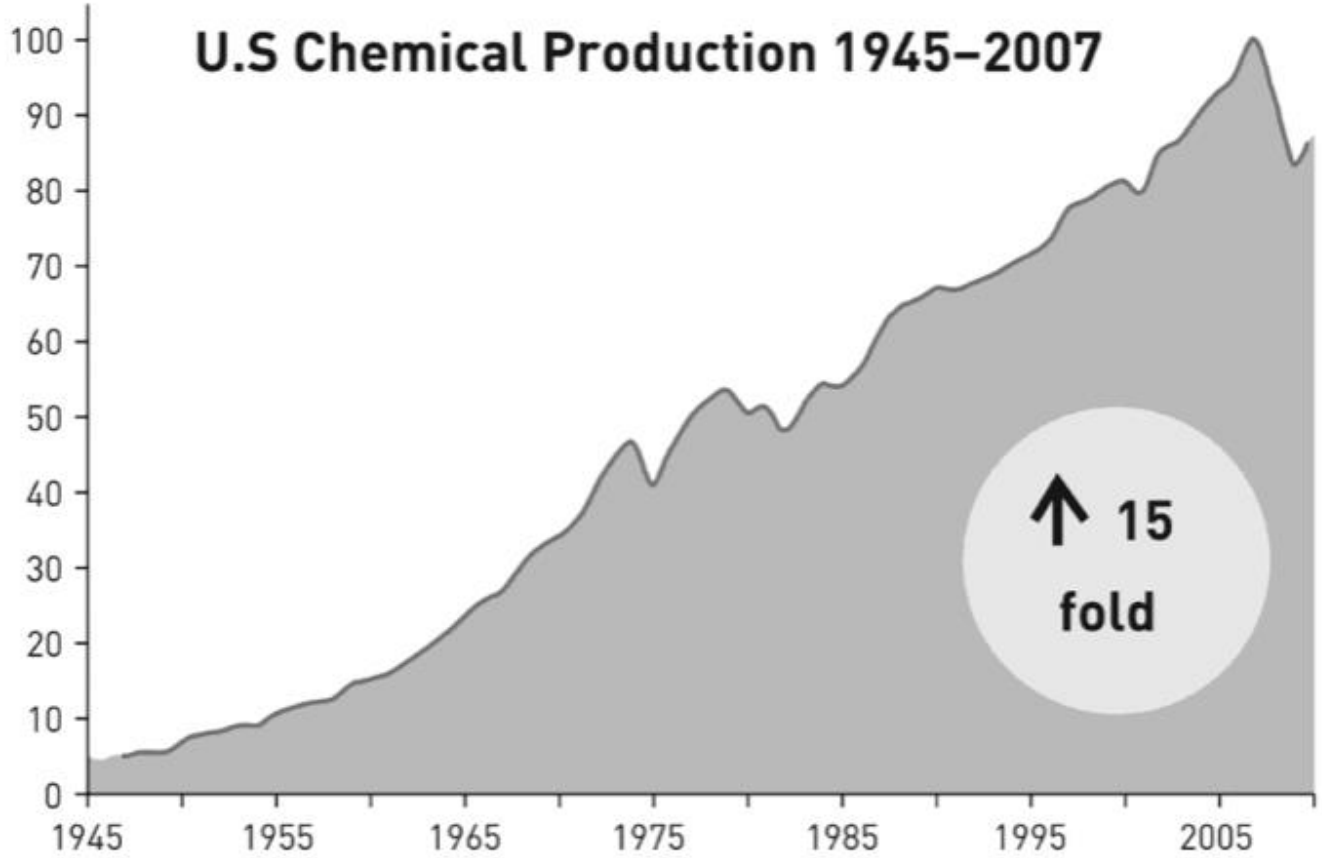

Swiffer
WETJET
FLOOR CLEANER
SAFE* ON ALL FINISHED FLOORS


ULTRA
Palmolive


A Family Company
glade
plugIns
LONGER LASTING
FRAGRANCE
LAVENDER
& VANILLA


More Soap, Longer
Brillo

JELL-O
Raid
Flying Insect
Life
CINNAMON
MULTIGRAIN CEREAL
PLANTERS
seventh generation
Yoplait
Florida's Natural
RUBY RED GRAPEFRUIT
Nature Made
Calcium
600 mg
WITH Vitamin D3 400 IU
DIETARY SUPPLEMENT
220 TABLETS
Long-Lasting Fragrance
CLOROX
SPLASH-LESS
MOTT'S
Applesauce
Colgate
50% more BONUS
method
ALL-PURPOSE
naturally derived surface cleaner
pink grapefruit
FRAGRANCE INFUSED WITH ESSENTIAL OILS
glade
LISTERINE
COOL MINT
FOR A FRESHER & CLEANER MOUTH THAN BRUSHING ALONE
KILLS OVER 100
Lysol
BANANA BOAT
KIDS SPORT
50
O·P·I
NAIL LACQUER
NEW SMOOTHER GLIDE
PANTENE
Aunt Jemima
Buttermilk
CAPE COD
Kettle Cooked Potato Chips
Mrs. MEYER'S
CLEAN
Breyers
Homemade Vanilla
diet pepsi
Honest tea
GOLDEN BLOSSOM HONEY
Premium U.S.
NET WT. 24 OZ.
Poland Spring



Federal reserve data on chemical production is only offerred as relative production, which is unit-less. A specific reference year is chosen and values are calculated relative to that years production. In this particular data set 2007 is the referencce year and is assigned a value of 100. Data from: U.S. Federal Reserve Board, Division of Research and Statistics

UCSF Program on Reproductive Health and the Environment

UCSF
University of California
San Francisco

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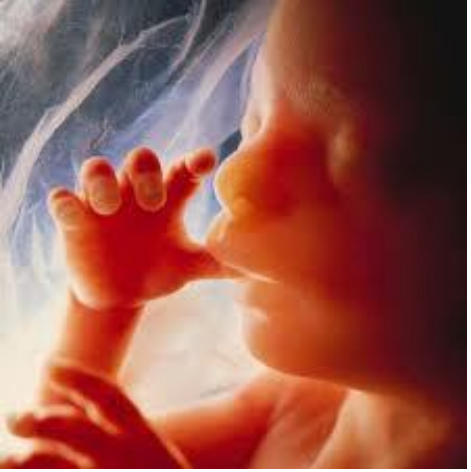
BLACK FLAG
ANT & ROACH KILLER
WATER BASED
ORTHO
HORNET


shutterstock

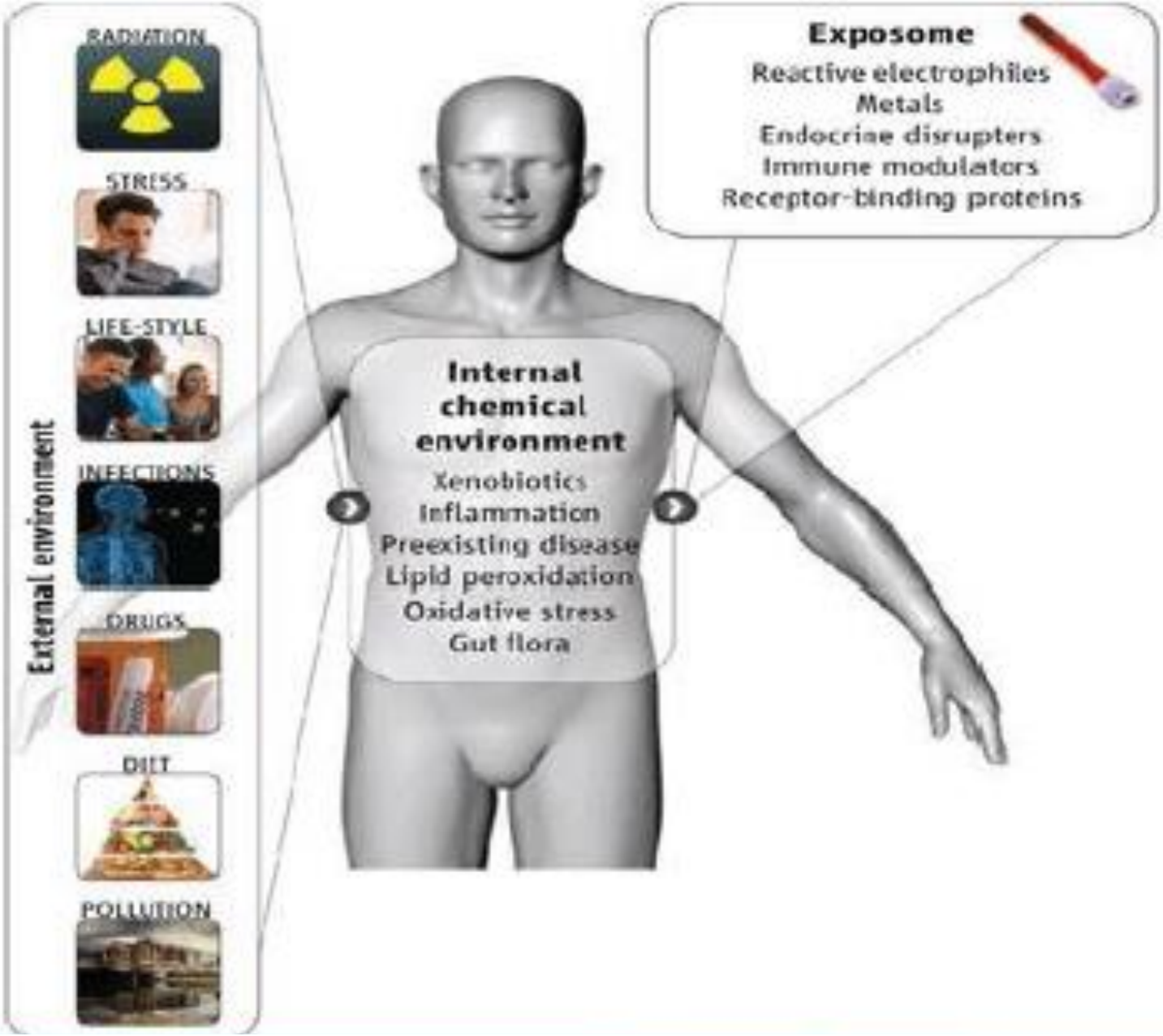
Definitions

- **Toxin** - a poison or venom produce or derived by certain bacteria, plants, insects or animals and causing disease when present at low concentration in the body.
- **Toxic –** a synthetic poison, *not* derived from a natural or living source
- **Poison -** a substance that is capable of causing the illness or death of a living organism when introduced or absorbed.
- **Bio-hazard -** a risk to human health or the environment arising from biological work, especially with microorganisms.
- **Adjuvant -** a substance that enhances the body's immune response to an antigen.
- **Xenobiotic -** substances that are foreign to the body or to an ecological system.
- **Dangerous Goods -** Dangerous goods, abbreviated DG, are substances that when transported are a risk to health, safety, property or the environment.



Environmental Chemicals

- Endocrine AND Immune disrupting chemicals
  - Thyroid dysfunction
  - Hormone sensitive cancers
  - Obesity
  - Insulin resistance
  - Hypertension
  - Reproductive/fertility dysfunction
- In-utero exposure:
  - Neurodevelopment
  - Cognition
  - Genitalia formation (cryptochidism)
  - Dimorphic sex differences of the brain
  - Transgenerational effects (gene edits)



Immune Mediated Inflammatory Disease (IMDS)

- **Synthetic chemicals** – BPA, phthalates, PFAs, metals, flame retardants
- **Natural products** – herbal products (ex. AILD)
- **Infections** - EBV, Covid, Zika (ex. GBS, Covid Long Haul)
- **Vaccines** – Rabies, HPV, Hep A/B, influenza, Covid (ex. GBS)
- **Medications** – DIL over 80 know medications (ex. minocycline, antihypertensives)

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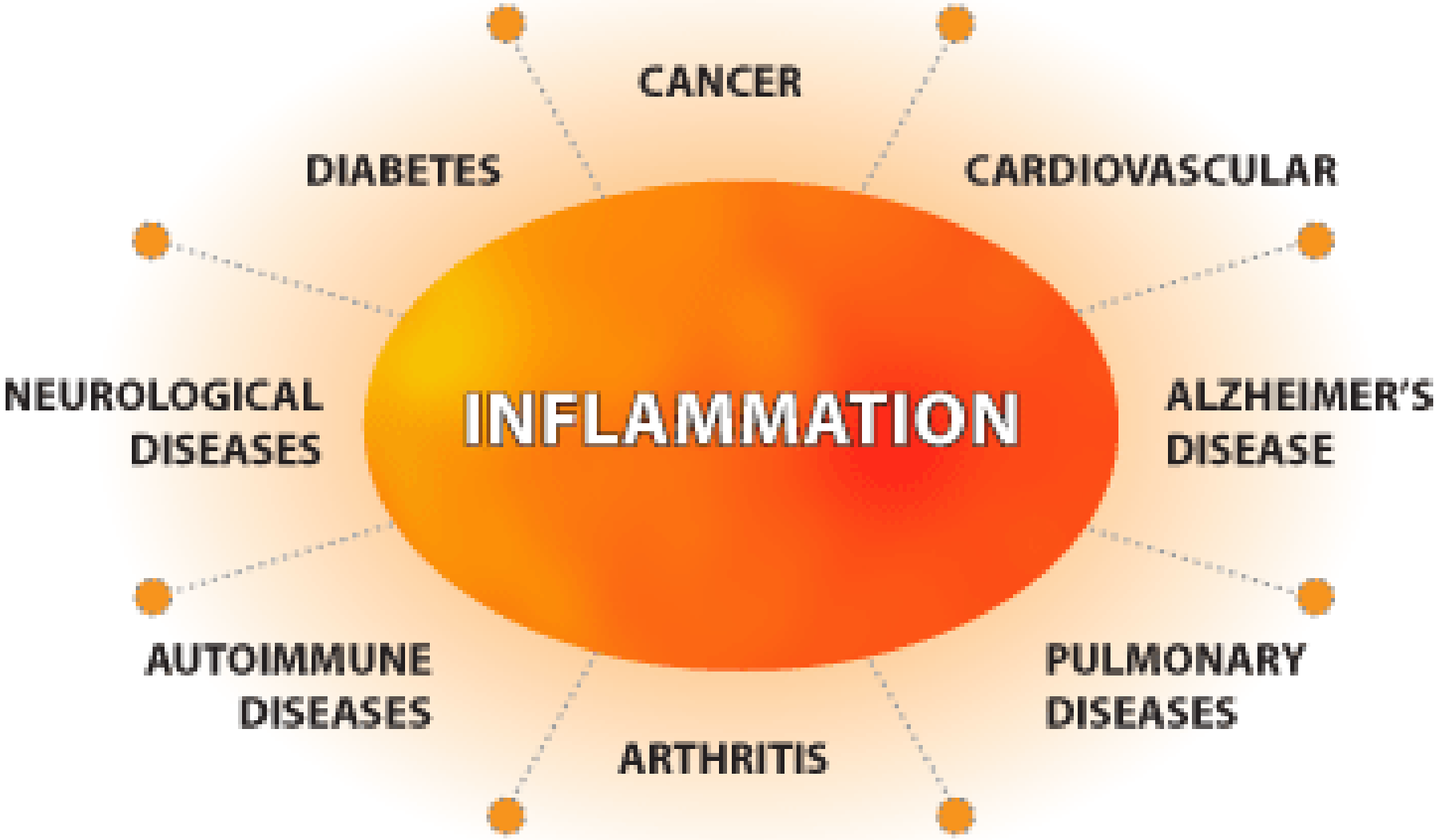
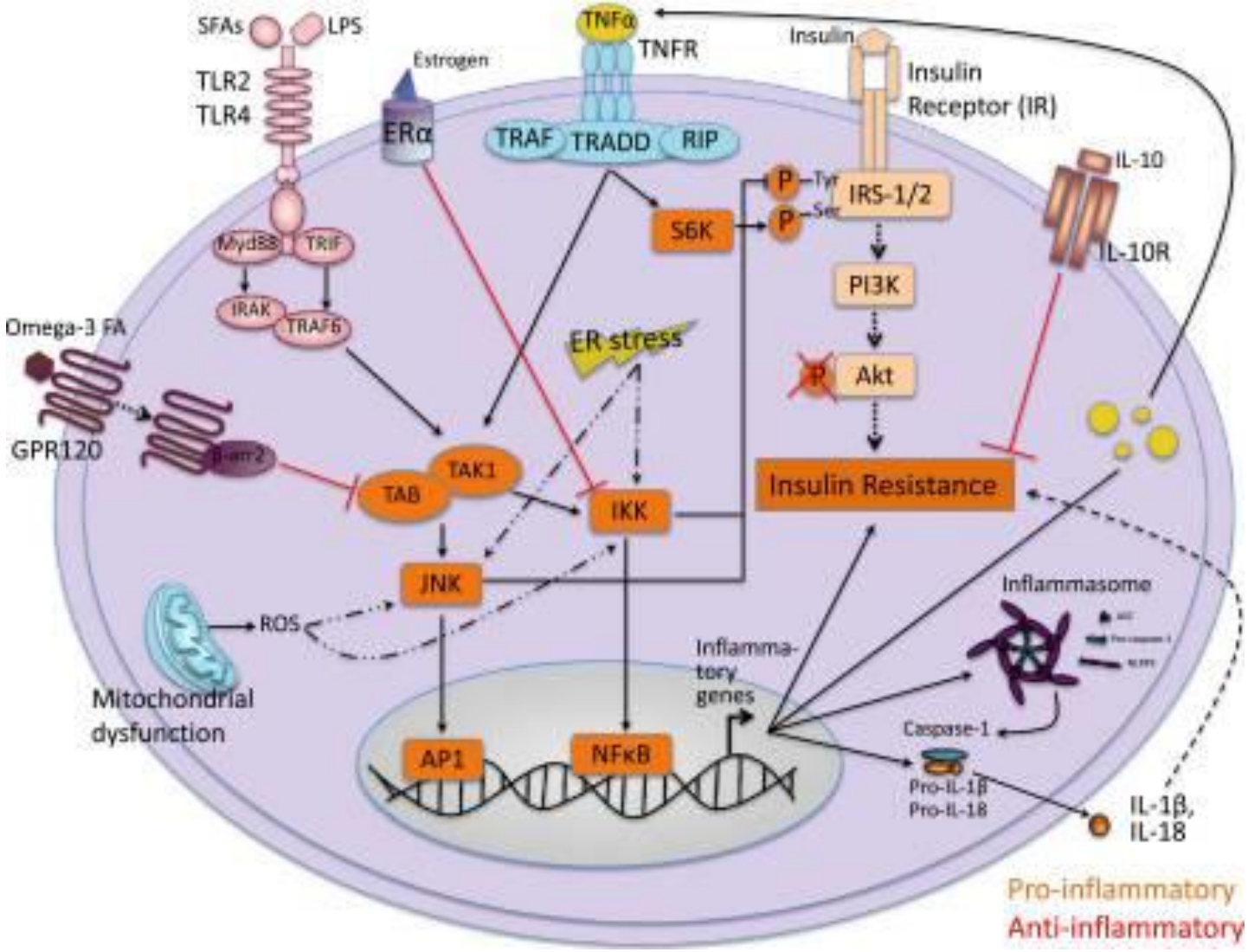
Autoimmune Disease (AID)

- Over 80 known
- Involve every human organ & cell type
- Epidemic rise in dozens of AID
- 3-10x greater in women than men
- Many factors associated with disease risk and development

Factors that Influence Clinical Disease

- **Exposure**
  - Known toxicity
    - Mechanism
    - Metabolites
  - Half-life
  - Involved organ
  - Additives/inert ingredients
  - Environmental conditions
  - Pseudo-persistence
- **Host**
  - Age
  - Gender
  - Comorbidities
  - Lifestyle
  - Gut health
  - Polypharmacy
  - Mixtures
  - Detoxification mechanisms
  - Genetic variability
  - Disease latency





Bansal A, Henao-Mejia J, Simmons RA. Immune System: An Emerging Player in Mediating Effects of Endocrine Disruptors on Metabolic Health. Endocrinology. 2018;159(1):32-45.

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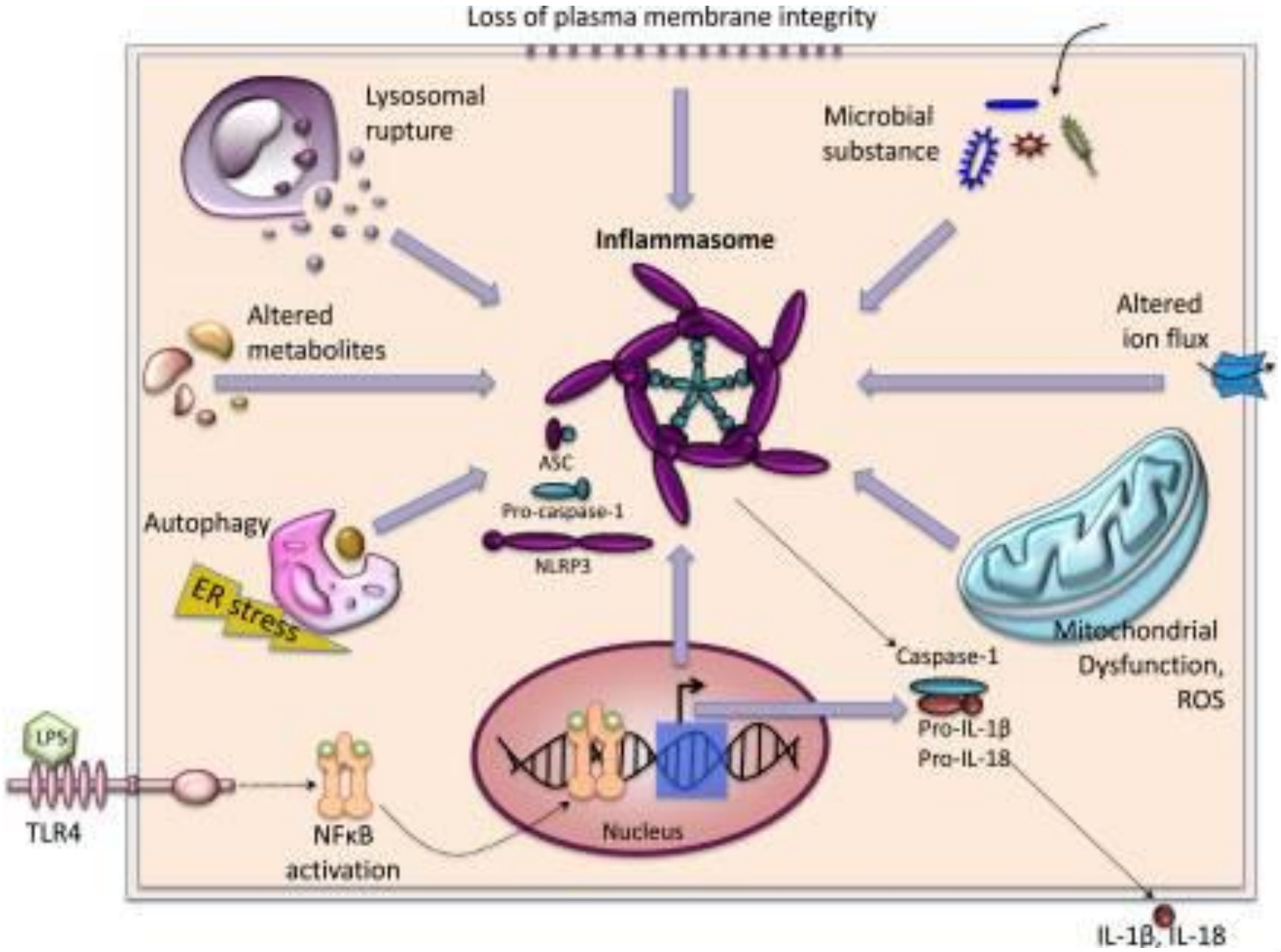

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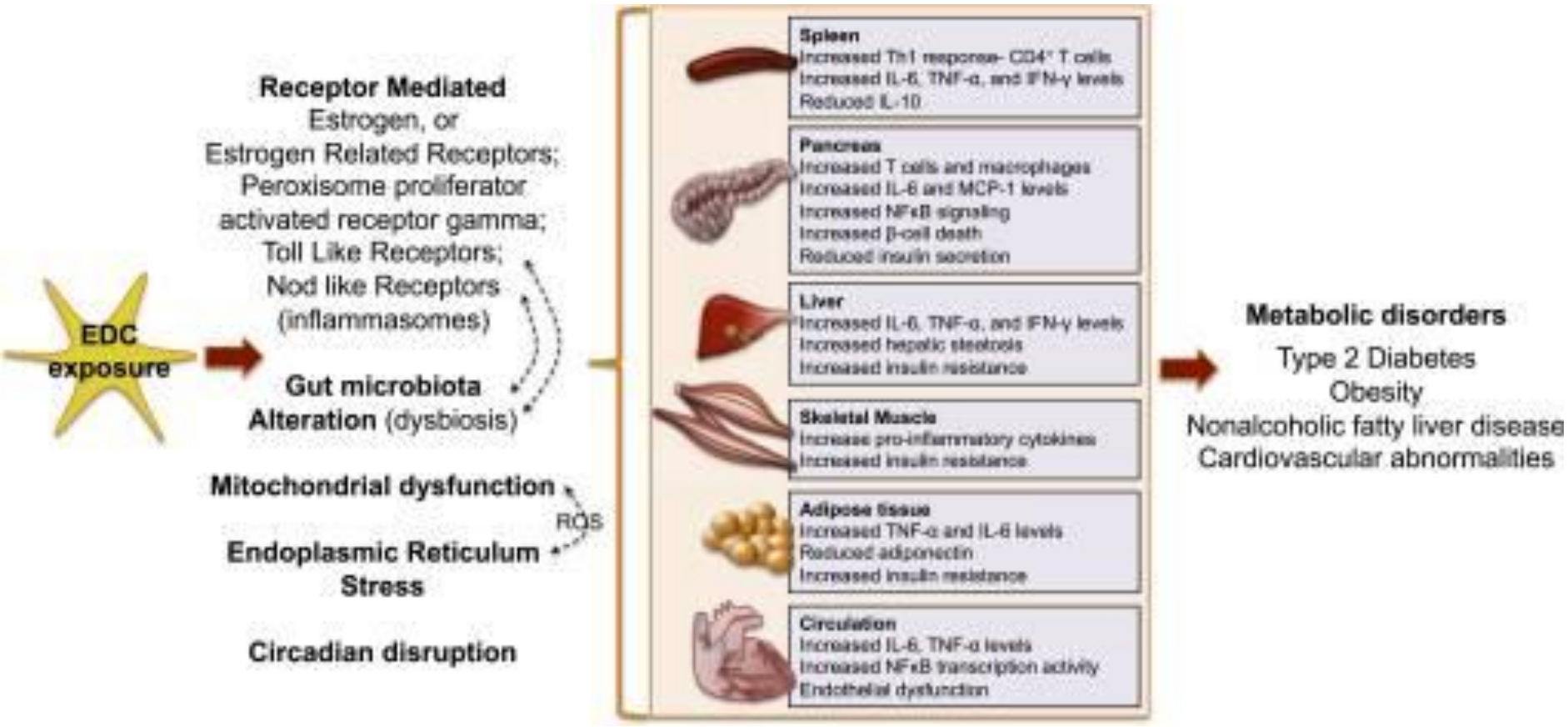

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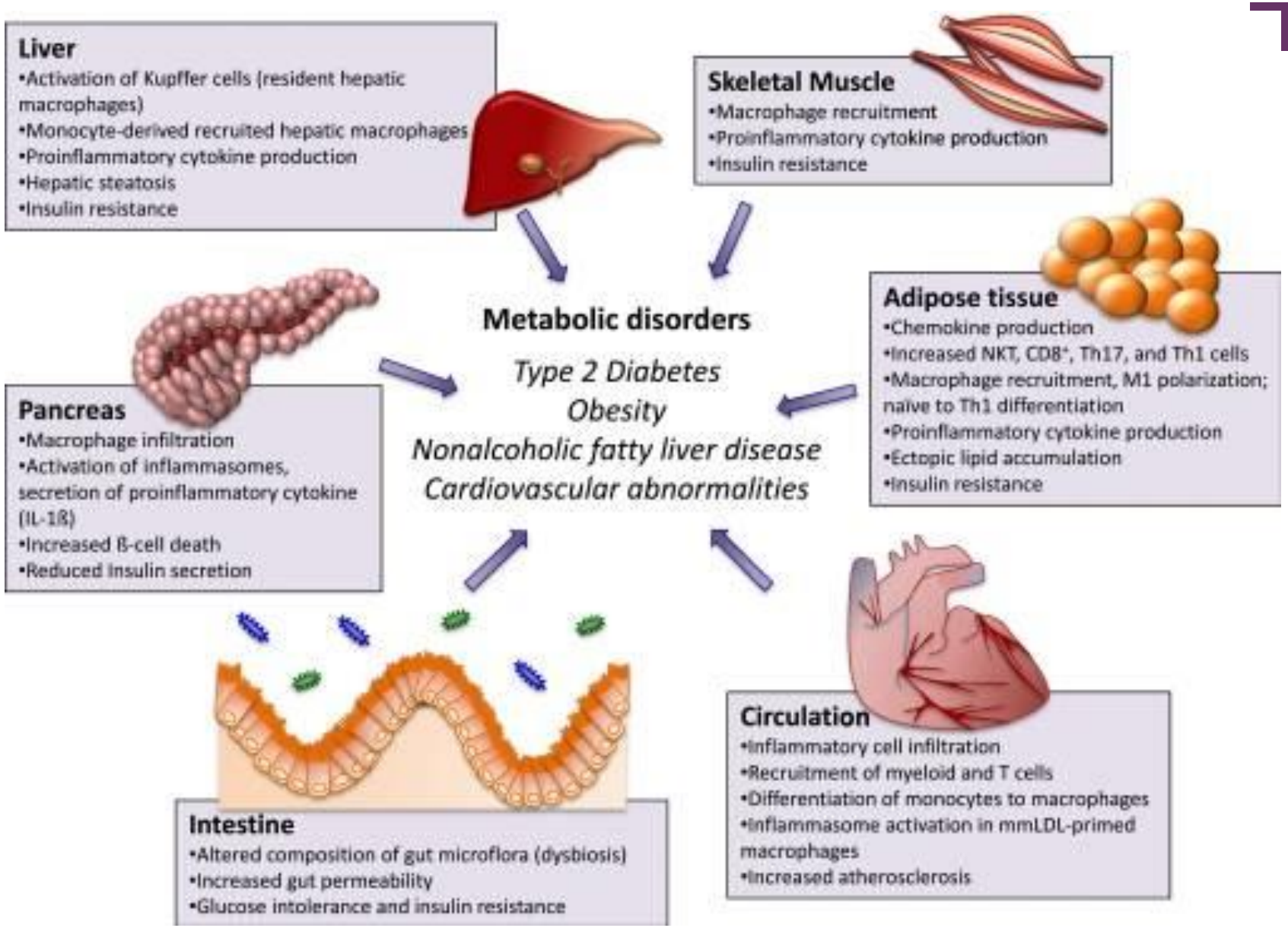

Bansal A, Henao-Mejia J, Simmons RA. Immune System: An Emerging Player in Mediating Effects of Endocrine Disruptors on Metabolic Health. Endocrinology. 2018;159(1):32-45.

Autoimmune Disease

- Genetic Predisposition (antecedents)
  - Family Hx
  - Genetic susceptibility
    - Haplotypes
      - HLA-B27 (AS, PSA)
      - HLA DQ2/8 (celiac)
      - HLA-DR1 & HLA-DR4 (RA)
- Environmental triggers
  - Toxins (metals, mycotoxins, food/water chemicals, industrial chemicals, EDCs, medications)
  - Microbes (bacteria, viruses, parasites, yeast, prions)
  - Stress (emotional, physical, synthetic light, noise pollution, EMF)
  - Poor sleep (reduced "clearance time")
- Permeability and the Biological terrain (mediators)
  - Zonulin, "leaky gut", reduced SCFA & butyrate
  - IgA deficiency
- Perpetuators of inflammations (mediators)
  - Poor diet (sugar, food additives, water contaminants, nutrient intake)
  - Stress, sleep
  - Infection
  - Medications

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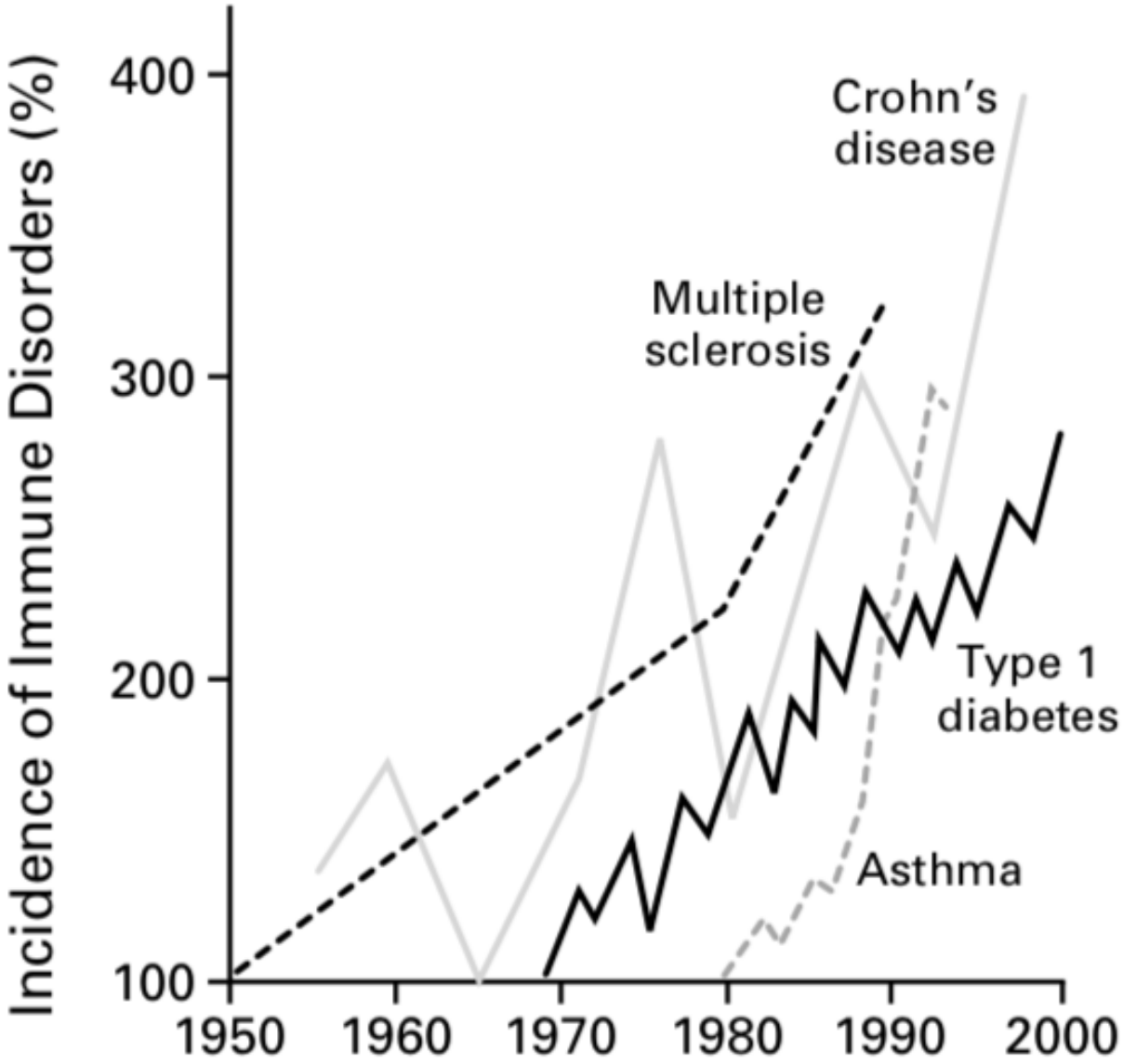


Bach et al. NEJM 2002 vol 347 pp 911-920.

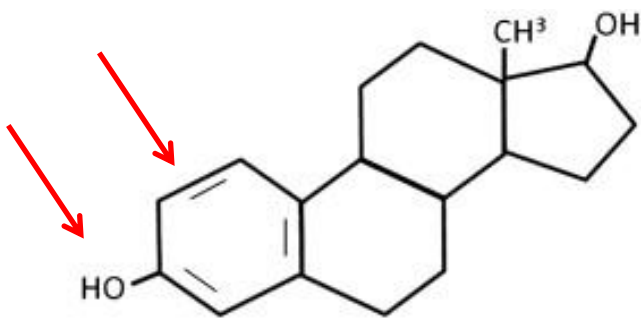
Mechanisms for AID

- **Molecular mimicry** – cross-reactive immune response against *self*-antigen
- **NLRP3 inflammasome** – vital role in both innate and adaptive immune system
- **Autophagy –** lack of clearance (ex. SLE)
- **Apoptosis –** lack of kill signal
- **Loss of self tolerance –** seen with natural aging
- **Background 'noise'–** baseline level of inflammation (tinder)

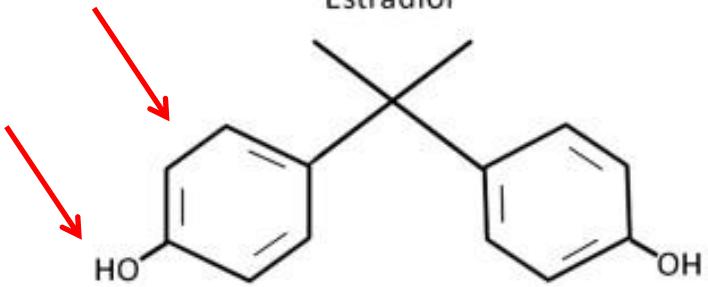
Case #1

- 47-year-old obese woman with Hx of Hashimoto's x 15 years
- BMI 36
- +TPO Abs / NL TSH and T3 and T4 now /elevated CRP / NL ESR
- On 88 mcg Synthroid
- Environmental Hx:
  - Multiple ABX as a child
  - Poor diet – 2-3 canned products ingested per day
  - ++BPA level on urinalysis

Bisphenol-A (BPA)

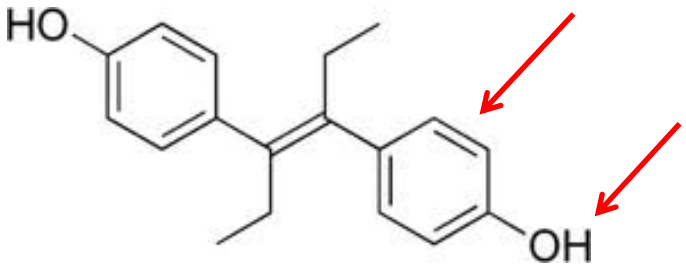


Estradiol

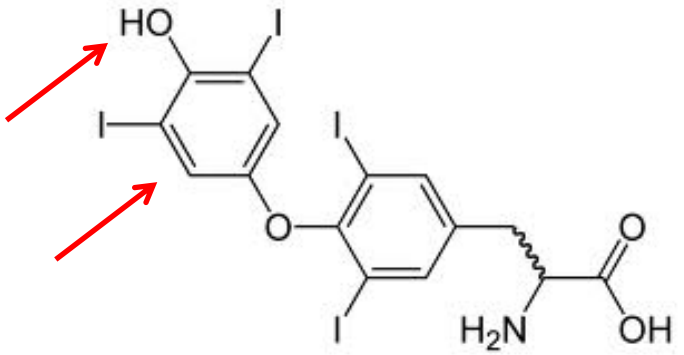


Bisphenol A

Two hydroxylated phenolic rings



Diethylstilbestrol (DES)

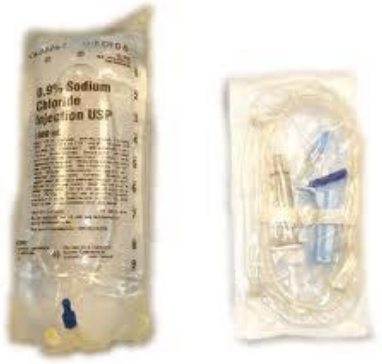


Thyroxine

BPA: Uses

- Added to the epoxy lining of cans to prevent contact with metal and corrosion
- Used to set ink on thermal receipts
- Added to polycarbonate plastics for rigidity
- General additive to other plastic products, including medical devices
- Used as a sealant in dental procedures

Sources of BPA



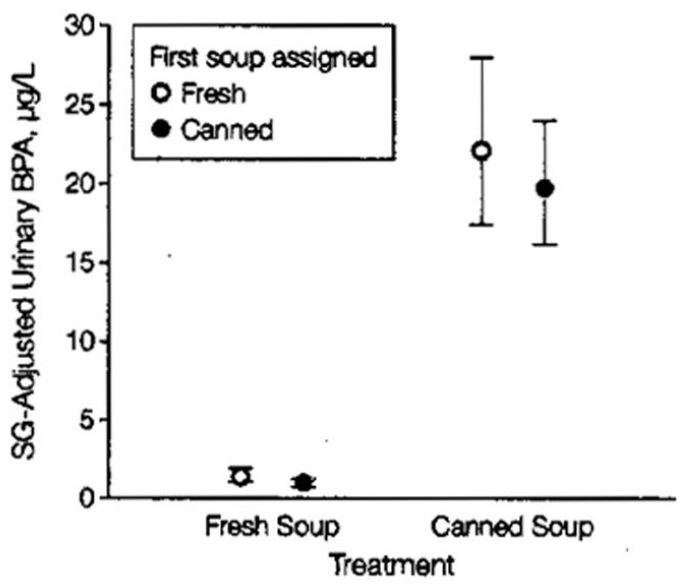
- Plastic bottles (polycarbonate)
- Food cans
- Soda cans
- Baby formula containers
- Store receip
- Printer ink
- Currency

- Dental amalgams, sealants and fillings
- PVC piping
- Blood bags/medical tubing
- Dust
- Recycled paper
- Paint

Avoiding Exposure: Food Choice Matters

- 2011 Harvard crossover study of 75 participants who either ate canned or freshly prepared soup, then switched.
- Conclusion: "Consumption of 1 serving of canned soup daily over 5 days was associated with a more than 1000% increase in urinary BPA."
- The public can reduce dietary exposure to BPA by choosing fresh food over canned food

Figure



Carwile JL, Ye X, Zhou X, Calafat AM, Michels KB. Canned soup consumption and urinary bisphenol A: a randomized crossover trial. JAMA. 2011 Nov 23;306(20):2218

Hindawi Publishing Corporation
Autoimmune Diseases
Volume 2014, Article ID 743616, 12 pages
http://dx.doi.org/10.1155/2014/743616

Review Article

The Potential Roles of Bisphenol A (BPA) Pathogenesis in Autoimmunity

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Bisphenol A (BPA) is a monomer found in commonly used consumer plastic goods. Although much attention in recent years has been placed on BPA's impact as an endocrine disruptor, it also appears to activate many immune pathways involved in both autoimmune disease development and autoimmune reactivity provocation. The current scientific literature is void of research papers linking BPA directly to human or animal onset of autoimmunity. This paper explores the impact of BPA on immune reactivity and the potential roles these mechanisms may have on the development or provocation of autoimmune diseases. Potential mechanisms by which BPA may be a contributing risk factor to autoimmune disease development and progression include its impact on hyperprolactinemia, estrogenic immune signaling, cytochrome P450 enzyme disruption, immune signal transduction pathway alteration, cytokine polarization, aryl hydrocarbon activation of Th-17 receptors, molecular mimicry, macrophage activation, lipopolysaccharide activation, and immunoglobulin pathophysiology. In this paper a review of these known autoimmune triggering mechanisms will be correlated with BPA exposure, thereby suggesting that BPA has a role in the pathogenesis of autoimmunity.

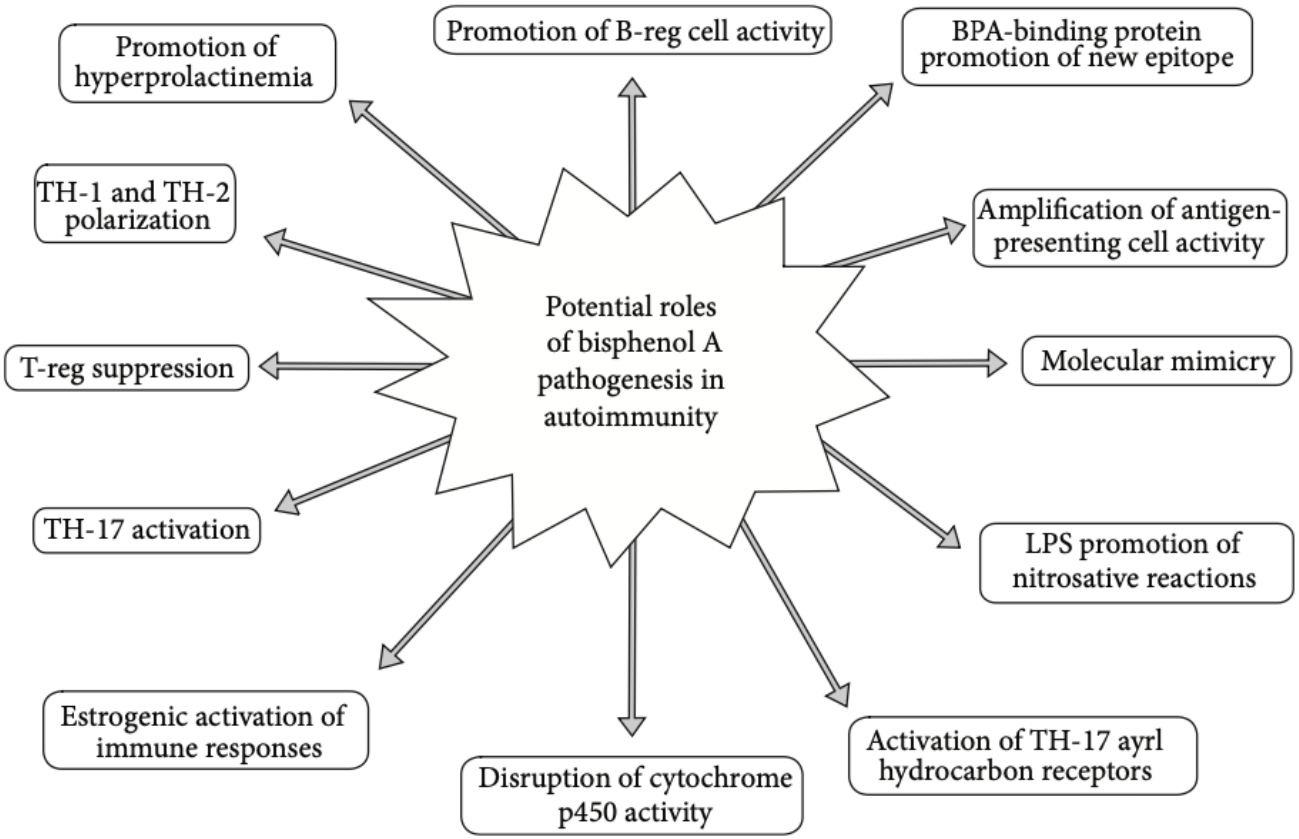

FIGURE 1: This diagram illustrates the potential mechanisms of bisphenol A's promotion of autoimmunity. BPA: bisphenol A; B-reg cell: regulatory B cell; LPS: lipopolysaccharide; TH: T-helper; T-reg: regulatory T cell.

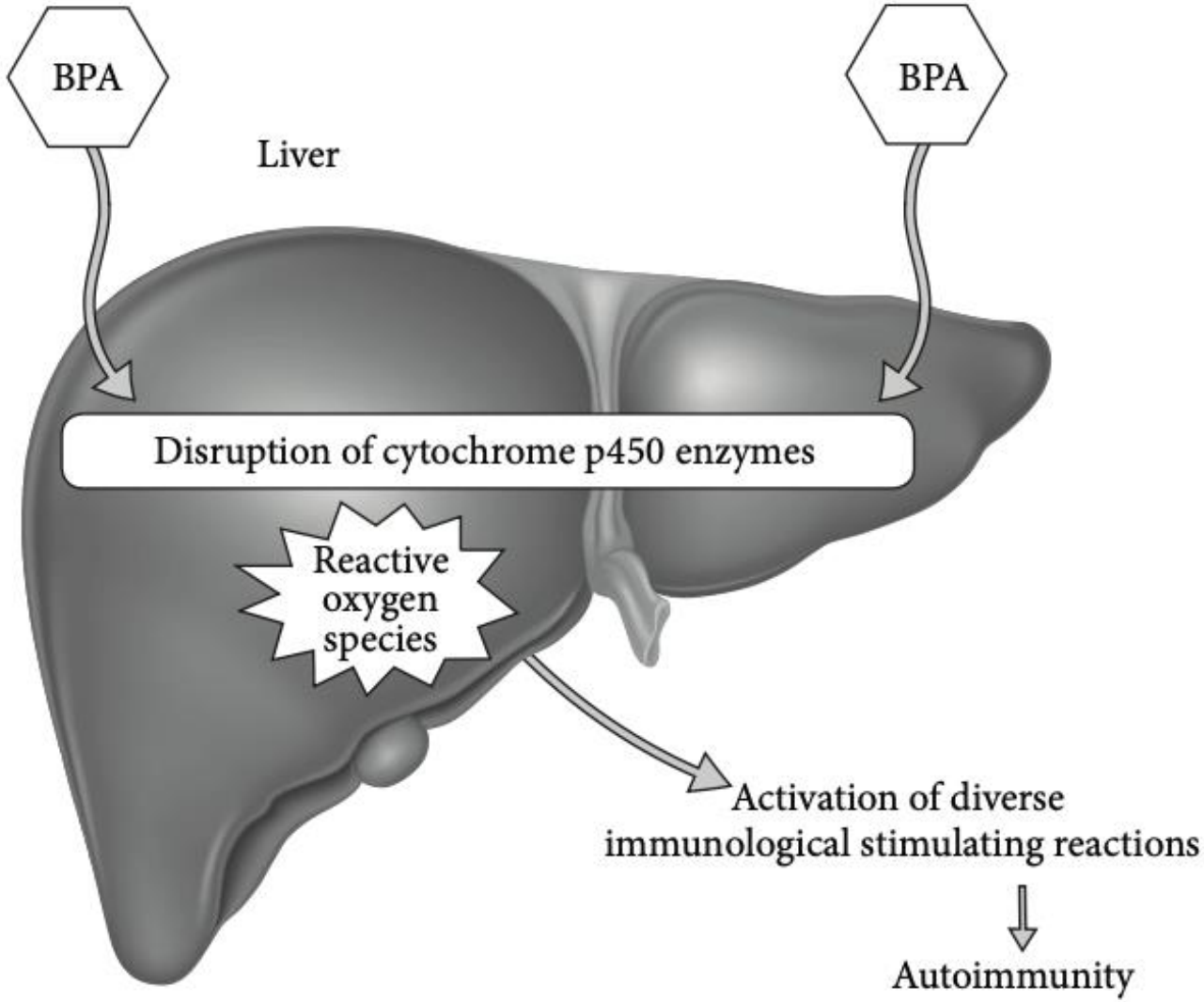

FIGURE 3: This diagram illustrates how bisphenol A can activate autoimmunity by disrupting cytochrome P450 enzymes. BPA: bisphenol A.

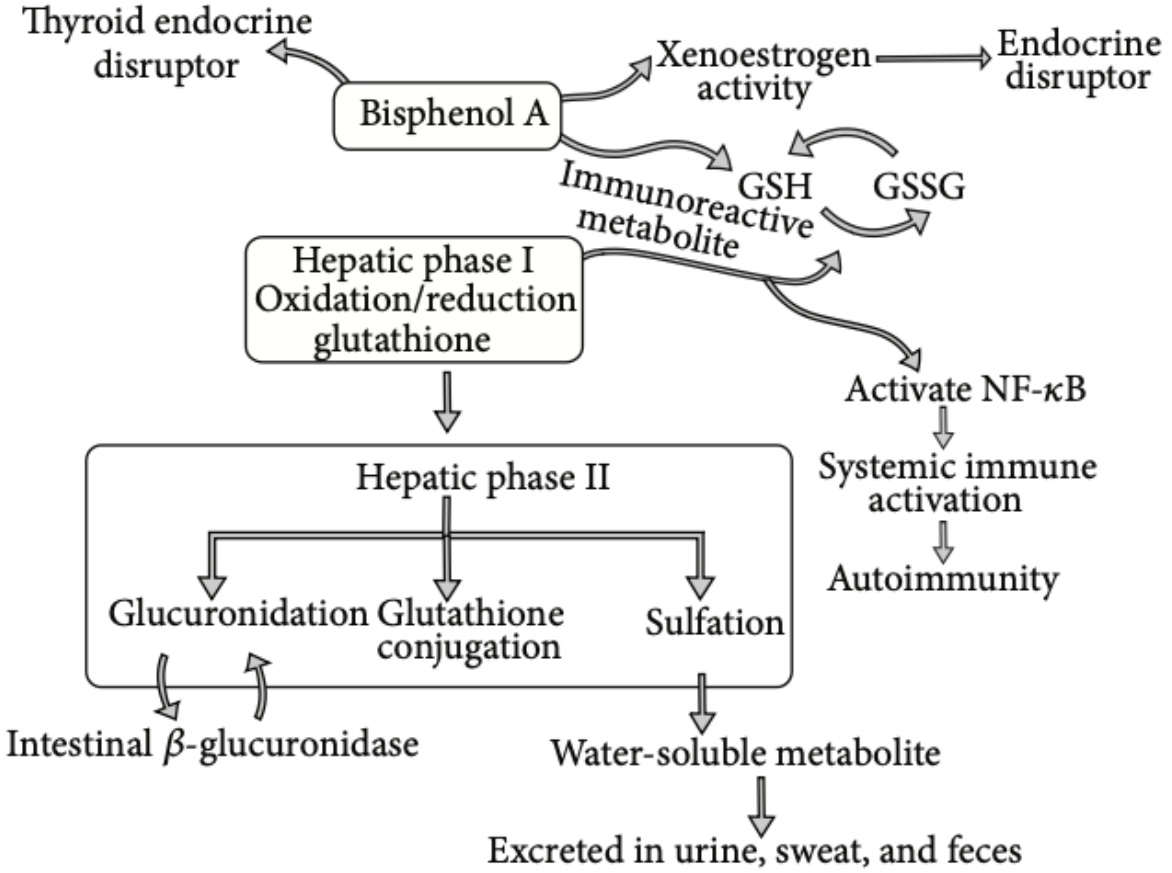

FIGURE 2: This diagram illustrates the hepatic biotransformation of bisphenol A. GSH: reduced glutathione; GSSG: oxidized glutathione.

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Full length article

Environmental endocrine disruptor Bisphenol A induces metabolic derailment and obesity via upregulating IL-17A in adipocytes

Xu Hong [a,1], Yi Zhou [a,1], Zhiyuan Zhu [a], Yuting Li [a], Zuo Li [a], Yuheng Zhang [a], Xinxin Hu [a], Fuhai Zhu [b], Yong Wang [c], Mingliang Fang [d], Yichao Huang [e,*], Tong Shen [a,*]

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[e] Department of Toxicology, School of Public Health, Anhui Medical University, Hefei 230032, Anhui, PR China

Case #2

- 67-year-old male with male breast cancer, no family hx
- Poor diet, no family Hx of breast CA, neg for BRCA genes
- Worked on a contaminated military site from 1978-1983
- Drank contaminated well water

Camp Lejeune

- Marine Corps Base Camp Lejeune is a 246-square-mile United States military training facility in Jacksonville, NC
- 1,000,000 drank the water b/t 1953-1987
- Covers 159,000 acres, 6 water treatment facilities, 7,690 buildings, largest marine base on the East Coast
- Studied by the National Academy of Sciences
- Water tested by Grainger Labs
- Vaporized over ground water contamination plume into homes (act like a tent)….worse in high heat/Summer
- PCE – tetrachloroethylene or PERC- 20x over permissible limit/TCE – trichloroethylene – 280x over the limit
- Childhood leukemia, kidney cancer, male breast cancer, fetal demise, congenital abnormalities
- Benzene also found from a spill/storage leak

U.S. Military Bases

- >130 TCE- contaminated military sites found – thus, the U.S. Department of Defense is the nation's largest polluter
- TCE is one of the most common contaminants found at Federal Superfund sights…> 2000…non-Superfund sites (regulated under state programs)
- Approximately 1 in 10 Americans lives within 10 miles of a contaminated military site
- PFAS or perfluoroalkyls - "forever chemicals" found in >300 military bases across the U.S.
- Many bases use well water

TCE - trichloroethylene

- First developed in 1864 by Dr. E. Fischer of Neustreitz, Germany…not utilized for commercial use for over 40 years
- Used as a solvent as a de-greaser, in dry cleaning, textiles, varnishes, paints, medical applications, food industry to extract fats from soy-beans and other plants
- Degreasing - predominant use: non-corrosive, rapid evaporation, non-flammable, ease of recycling
- TCE became a "known carcinogen" in 2016 under TOSCA – Toxic Substances Control Act
- Listed by IARC (Group 1) and NTP (15th report) as a "Known" carcinogen
- Effective 1989 USEPA MCL for TCE in drinking water was set at 5 parts per billion (ppb)

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TCE Production

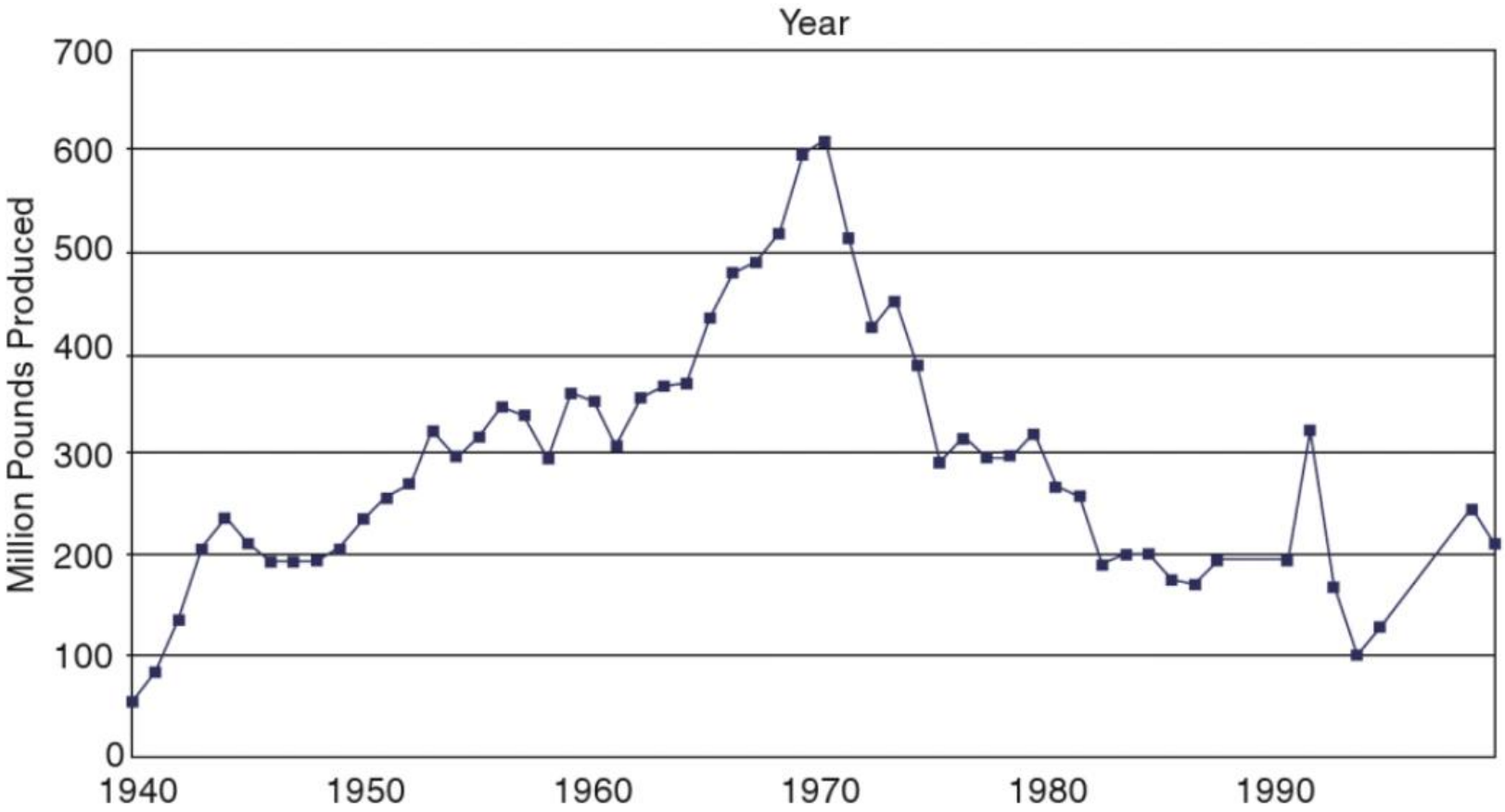

Fig. 1.1 US production of TCE (Doherty 2000; Lee et al. 2003; Leppart 1945)

TCE

- Autoimmune hepatitis (AIH)
- Parkinson's Disease
- SLE
- Multiple sclerosis
- Rheumatoid arthritis
- Scleroderma (systemic sclerosis)
- Cancers

TCE

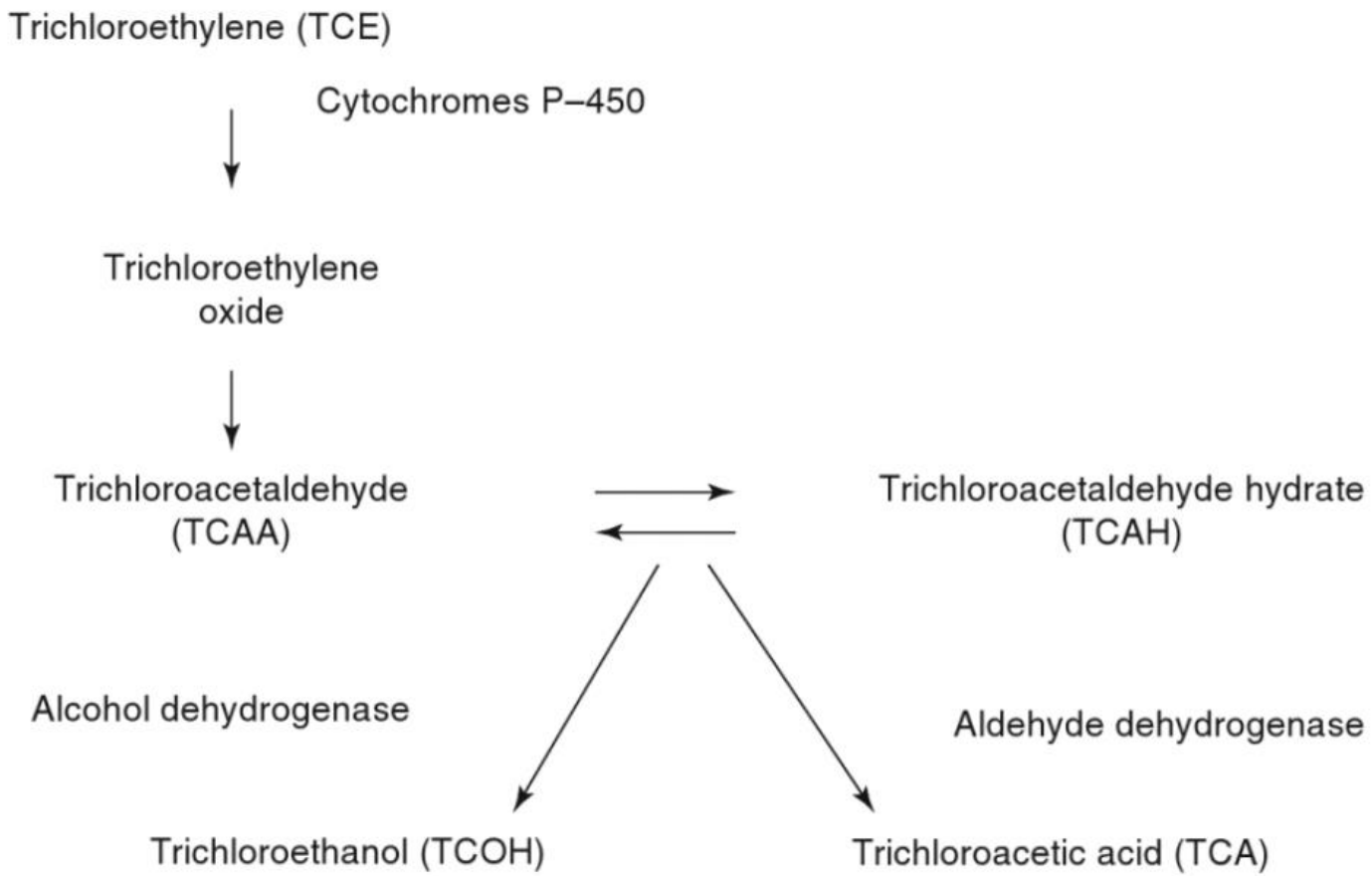

Fig. 2.1 Metabolism of trichloroethylene

Ramdhan et al. 2008

TCE

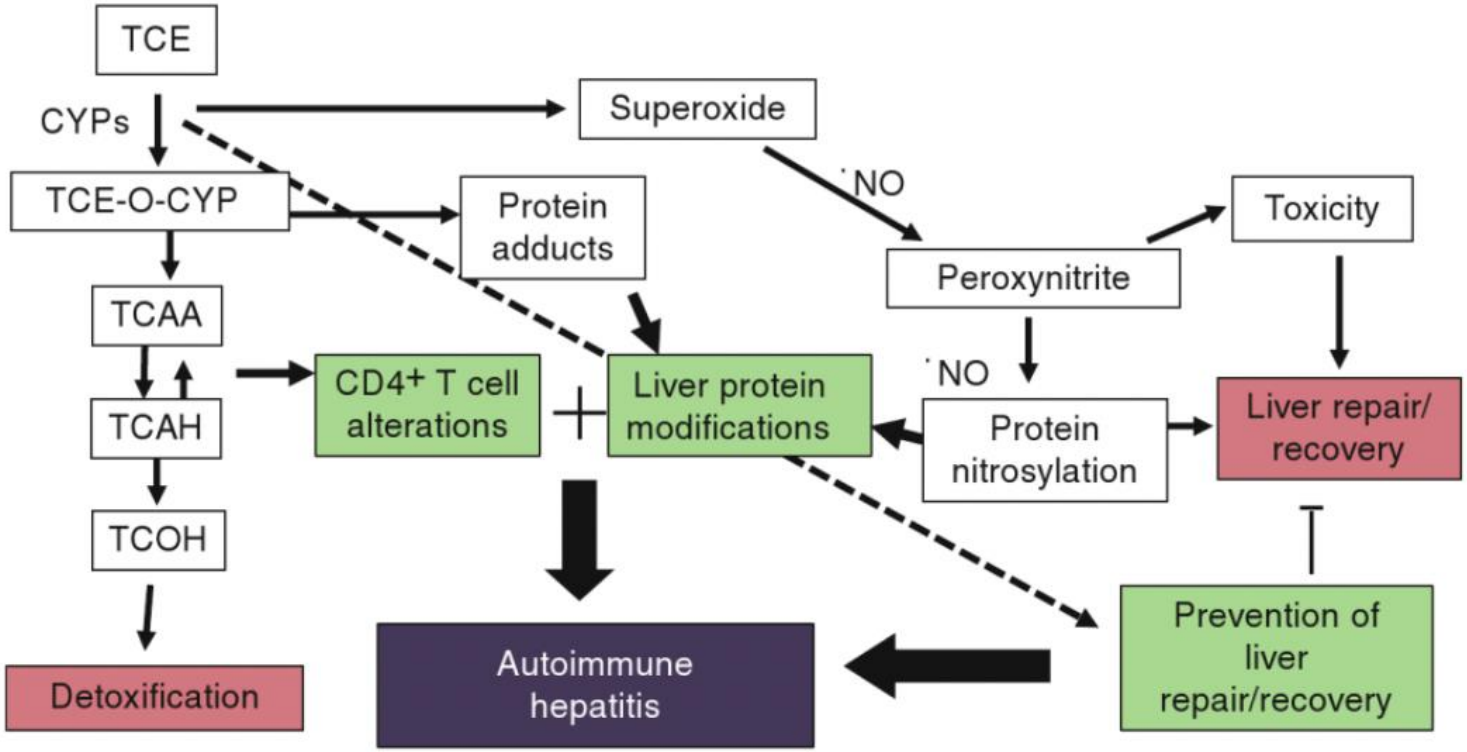

Fig. 2.2 Possible mechanism of TCE-induced autoimmune hepatitis

Gilbert, Kathleen, Blossom, Sarah, Trichloroethylene: Toxicity and Health Risks, Humana Press, London 2014.

TCE and AID

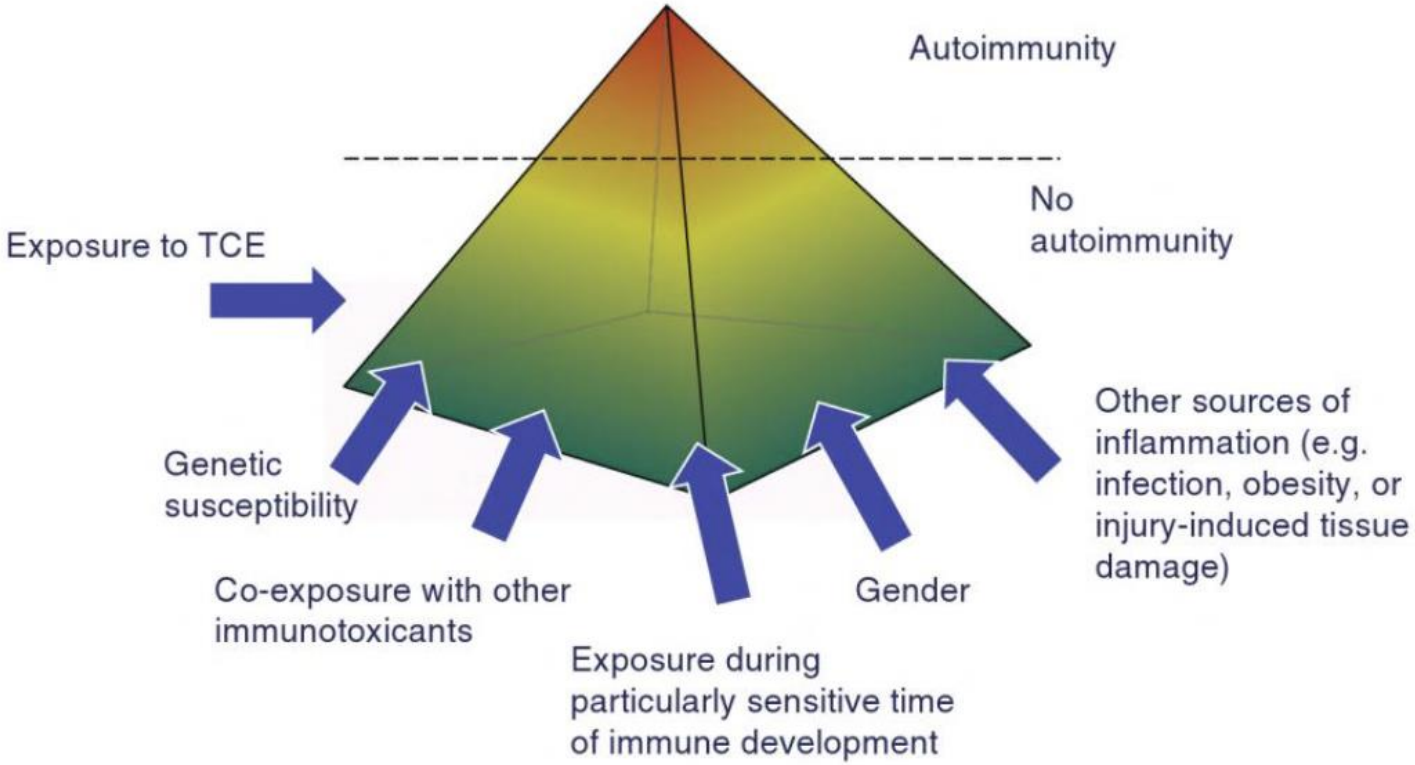

Fig. 2.3 Possible contributors to TCE-induced autoimmune disease

Gilbert, Kathleen, Blossom, Sarah, Trichloroethylene: Toxicity and Health Risks, Humana Press, London 2014.

Apoptosis

- Studied on MRL+/+ (young female) mice, predisposed to the development of SLE
- Activation-induced apoptosis is preprogrammed cell death- a protective, evolutionary mechanism that stops the expansion of autoreactive CD4+ T cells
- Defects in this process have been linked to the development of several idiopathic autoimmune disease such a systemic lupus erythematosus, MS, and RA in both humans and mice.
- Therapies that facilitate Fas-mediated T-cell apoptosis can ameliorate autoimmune disease

Metabolism

- The toxicity of any chemical requires their metabolism
- TCE can be metabolized by both kidney and liver in mice and humans…Majority is metabolized by the oxidative pathway in the liver
- Cytochrome P450s (CYPs) rapidly converts TCE to trichloroacetaldehyde hydrate (TCAH)…multiple other steps.
- The level of TCAH depends on the activity of several metabolizing enzymes (ex. CYP2E1, CYP1A1), all of which display considerable genetic variation in both humans and mice
- Many of the CD4+ T cell modulating effects of TCE are induced by its metabolite TCAH

Schiff Base Formation

- The structure of TCAH, which is an aldehyde, has the capacity to form a chemical rxn known as Schiff base, a transient covalent bond between nucleophiles on proteins (eg. Amino group on lysine) and electrophilic carbonyl carbons on aldehydes.
- Schiff base formation is the foundation of the stimulatory interactions that normally occur between specific molecules on the CD4+ T cell surface and associated ligands on the surface of accessory cells such as dendritic cells on endothelial cells.
- These interactions between CD4+ T cell and accessory cells are crucial for CD4+ T cells activation and effector function
- Certain small Schiff-base-forming compounds (ex. TCE) may be able to bypass the need for ligand-bearing accessory cells and co-stimulate CD4+ T cells directly

Organ Events

- Formation of chemically-modified self proteins capable of triggering an immune response
- Balance: nitrosative/oxidative stress not balanced by the appropriate detoxification by various antioxidant compounds (ex. glutathione, vitamin E) and enzymes (ex. glutathione peroxidase)…free radicals, lipid peroxidation, protein tyrosine nitration, increased inducible nitric oxide synthase (iNOS), which produces nitric oxide0DNA damage, and cell death are produced

Rheumatoid Arthritis

Rheumatoid Arthritis

- An autoimmune disease, targets joints, causing pain, inflammation and joint destruction
- Can affect all joints-including hands, wrists, knees shoulders and spine, often symmetrical presentation (C-spine, voice box)
- Long-standing or untreated RA can lead to organ damage

Rheumatoid Arthritis

- RA is the most common form of inflammatory, autoimmune arthritis, affecting 1.5 million in the U.S.… 0.5-1% worldwide…and increasing!
- About 75% of those affected by RA are women
- 1–3% of women may develop RA in their lifetime
  - Symptoms improve with pregnancy
- RA most often begins between the ages of 40-60, however, it can develop at any age
- T-helper-1, cytokine-mediated condition
- "Unknown" cause

Influences on RA Development

- Gut microbiome/oral microbiome (periodontal disease)
- Cold environment
- Adult and Childhood 1st & 2nd-hand smoke exposure
- Shift work
- Mediterranean diet (lowers risk)
- ETOH (lowers risk)
- Air pollution/Childhood secondhand smoke
- Oral contraceptives (raise or lower risk)
- Breast feeding (lowers risk)

Influences on RA Development

- Obesity
- Abdominal obesity (regardless of BMI)
- Low vitamin D
- Infection: COVID, EBV
- Chemicals (EDCs): BPA, phthalates, PCBs, flame retardants
- MEDS!!!
  - Androgen deprivation therapy (ADT) - prostate CA tx
  - Immune checkpoint inhibitors (ICIs)
  - Statins

RESEARCH ARTICLE

Pattern of risks of rheumatoid arthritis among patients using statins: A cohort study with the clinical practice research datalink

Hilda J. I. de Jong[1,2,3], Jan Willem Cohen Tervaert[4,5], Arief Lalmohamed[3,6], Frank de Vries[3,7,8], Rob J. Vandebriel[1], Henk van Loveren[1,2], Olaf H. Klungel[3]*, Tjeerd P. van Staa[3,9,10]

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Rheumatic immune-related adverse events from cancer immunotherapy

Leonard H. Calabrese[1], Cassandra Calabrese[1] and Laura C. Cappelli[2]*

Abstract | Immunotherapy has revolutionized the treatment of cancer, but a rapid rise in the use of the family of therapeutic agents known as checkpoint inhibitors (CPIs) is associated with a new group of immune-related adverse events (irAEs) in almost any organ system. Among these irAEs, rheumatic complications are common and seem to have features that are distinct from irAEs in other organ systems, including a highly variable time of clinical onset and the capacity to persist, possibly indefinitely, even after cessation of CPI therapy. In this Review, mechanisms of action of CPIs and how they might cause rheumatic irAEs are described. Also covered are epidemiology and clinical descriptions of rheumatic irAEs, plus guiding principles for managing irAEs. Finally, we outline future directions that must be taken in response to a series of unanswered questions and unmet needs that now confront rheumatologists who are, or will be, engaged in this new area of rheumatology.

Immune-related adverse events
(irAEs). A term now used commonly to describe the range of toxic effects in one or more organs after exposure to checkpoint inhibitors.

Immunotherapy has revolutionized the treatment of cancer and is now considered central to the clinical management[1]. The immunotherapy field is evolving rapidly, and although a variety of treatment modalities exist, including breakthroughs in cellular therapies, the most commonly used approach is to administer monoclonal antibodies that are specific for regulatory checkpoint molecules, that is, checkpoint inhibitors (CPIs). CPIs regulate T cell activation and effector function and are involving >100,000 patients are ongoing in the United States alone[8]. This Review provides a clinical overview of the most commonly reported rheumatic irAEs, emphasizing epidemiology and clinical manifestations. We also provide suggestions for collaborative management approaches, plus we frame rheumatic irAEs in the context of the broader spectrum of irAEs and discuss a possible immunopathogenic basis. Finally, we present an agenda of unsolved issues that need to be addressed

CURRENT OPINION

COVID-19 and autoimmune diseases

Yu Liu[a], *Amr H. Sawalha*[b], *and Qianjin Lu*[a,c]

Purpose of review

The aim of this study was to evaluate the relationship between infection with SARS-CoV-2 and autoimmunity.

Recent findings

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by severe acute respiratory syndrome (SARS) associated coronavirus 2 (SARS-CoV-2). Although most of the infected individuals are asymptomatic, a proportion of patients with COVID-19 develop severe disease with multiple organ injuries. Evidence suggests that some medications used to treat autoimmune rheumatologic diseases might have therapeutic effect in patients with severe COVID-19 infections, drawing attention to the relationship between COVID-19 and autoimmune diseases. COVID-19 shares similarities with autoimmune diseases in clinical manifestations, immune responses and pathogenic mechanisms. Robust immune reactions participate in the pathogenesis of both disease conditions. Autoantibodies as a hallmark of autoimmune diseases can also be detected in COVID-19 patients. Moreover, some patients have been reported to develop autoimmune diseases, such as Guillain–Barré syndrome or systemic lupus erythematosus, after COVID-19 infection. It is speculated that SARS-CoV-2 can disturb self-tolerance and trigger autoimmune responses through cross-reactivity with host cells. The infection risk and prognosis of COVID-19 in patients with autoimmune diseases remains controversial, but patient adherence to medication regimens to prevent autoimmune disease flares is strongly recommended.

Liu Y, Sawalha AH, Lu Q. Curr Opin Rheumatol. 2021 Mar 1;33(2):155-162.

CTS Clinical and Translational Science
An Official Journal of ASCPT
Open Access

Clin Transl Sci. 2021 May; 14(3): 898–907.
Published online 2021 Jan 21. doi: 10.1111/cts.12953

PMCID: PMC8212749
PMID: 33306235

SARS-CoV-2 infection as a trigger of autoimmune response

Maria C. Sacchi,[1] Stefania Tamiazzo,[1] Paolo Stobbione,[2] Lisa Agatea,[3] Piera De Gaspari,[4] Anna Stecca,[3] Ernesto C. Lauritano,[5] Annalisa Roveta,[6] Renato Tozzoli,[7] Roberto Guaschino,[1] and Ramona Bonometti[5]

immunology
Immunology homepage
Insights into immunity in health and disease

REVIEW | Free Access

New-onset autoimmune phenomena post-COVID-19 vaccination

Yue Chen, Zhiwei Xu, Peng Wang, Xiao-Mei Li, Zong-Wen Shuai, Dong-Qing Ye ✉, Hai-Feng Pan ✉

First published: 27 December 2021 | https://doi.org/10.1111/imm.13443 | Citations: 6

Funding information

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Case #4

- 21 yo female with new onset joint pain and facial rash, ANA+ 1:1280, 8 months after uncomplicated Covid infection
  - No renal issues/blood clotting/cognitive issues
- Hx of severe EBV infection in high school
- Hx of sexual and emotional abuse as a child, +second and third-hand smoke exposure
- Poor diet, no supplements
- Taking oral minocycline for severe acne for 12 months

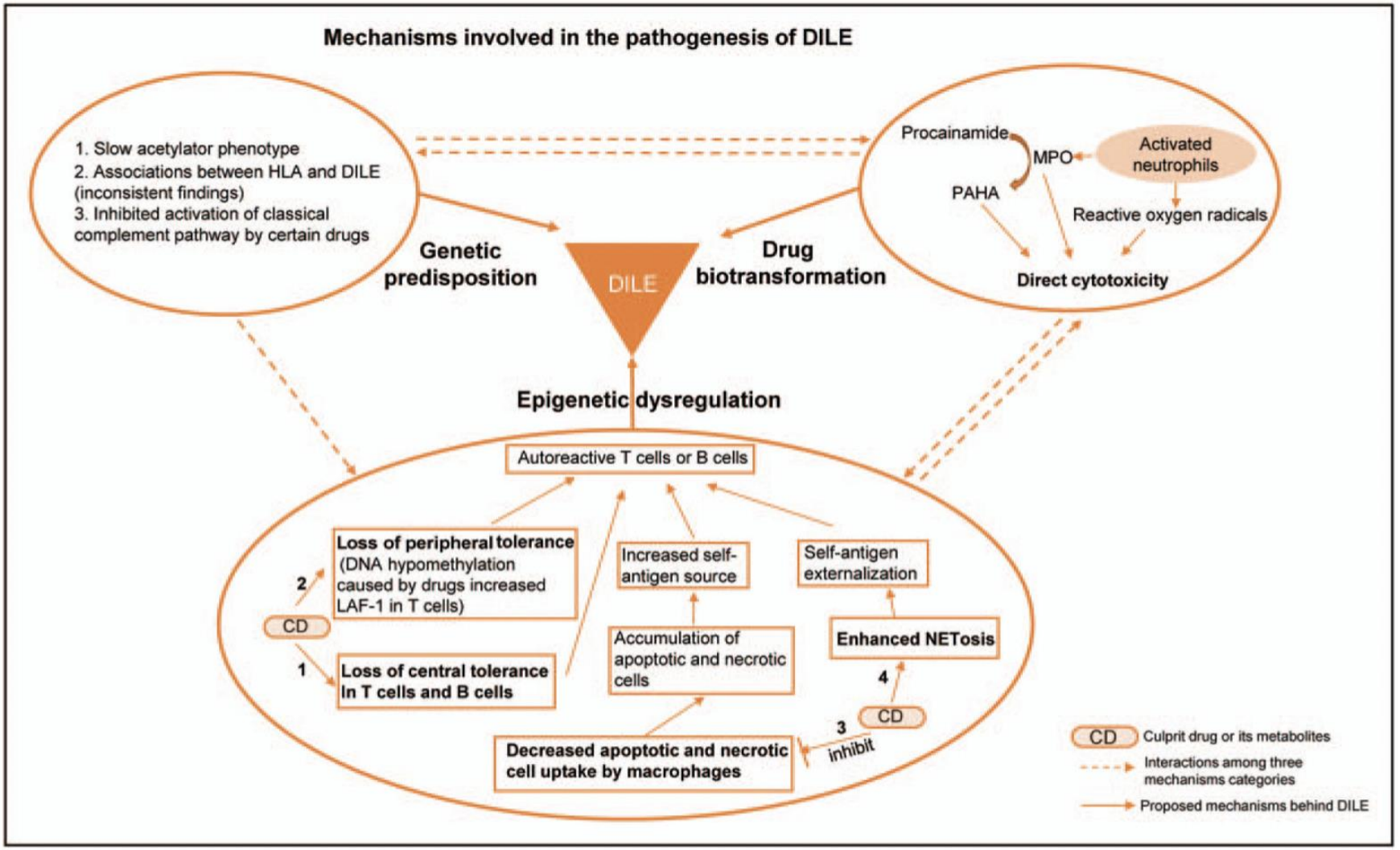
Drug-Induced Lupus (DIL)

Drug-Induced Lupus

Table 1 Drugs Reported to Have Induced Systemic Lupus Erythematosus.

Drug Group	High Risk	Moderate Risk	Low Risk	Very Low Risk
Antiarrhythmia agents	Procainamide (15%–20%)	Quinidine (< 1%)		Disopyramide, propafenone
Antihypertensives	Hydralazine (5%–8%)		Methyldopa, captopril, acebutolol	Clonidine, enalapril, labetalol, minoxidil, pindolol, prazosin, atenolol, timolol
Antipsychotic agents			Chlorpromazine	Chlorprothixene, lithium carbonate, phenelzine, perphenazine
Antibiotics		Isoniazid	Minocycline	Nitrofurantoin
Anticonvulsants			Carbamazepine	Ethosuximide, phenytoin, primidone, trimethadione
Antithyroid agents			Propylthiouracil	
Anti-inflammatory drugs		Sulfasalazine	D-penicillamine, sulfonamide	Phenylbutazone
Diuretics			5-aminosalicylic acid	Chlorthalidone, hydrochlorothiazide
Lipid lowering agents				Atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin
Biologic agents				Etanercept, infliximab, adalimumab, IFN-α, interleukin 2
Neuroleptic agents				Levodopa
Adrenal steroid inhibitors				Aminoglutethimide

Pretel M, Marquès L, España A. Drug-induced lupus erythematosus. Actas Dermosifiliogr. 2014 Jan-Feb;105(1):18-30. English, Spanish. doi: 10.1016/j.ad.2012.09.007.



He Y, Sawalha AH. Drug-induced lupus erythematosus: an update on drugs and mechanisms. Curr Opin Rheumatol. 2018 Sep;30(5):490-497.

Integrative Approaches

Integrative Rheumatology

Combines the best of **BOTH** conventional and integrative medicine techniques for pain control, disease management, overall well-being.

"*primum non nocere*"…. first, do no harm!!!

- Diet
- Exercise
- Stress management & breathing
- Biofeedback
- Acupuncture/Reiki
- Massage
- Physical therapy/OT
- Limit medication/USE medication
- Limit harmful environmental chemical exposures
- Appropriate use of supplements

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Need a great history!!!!

dietary (food AND water), meds, supplements
psychiatric, physical activity, sleep, stress,
occupational, home environment e.g.

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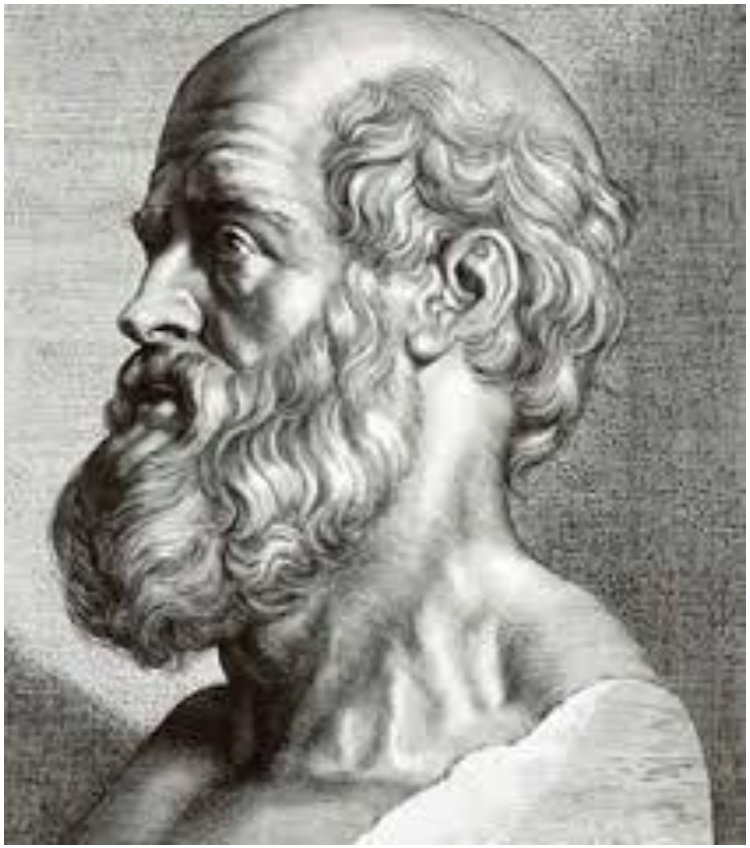
Diet



‘Let food be thy medicine and medicine be thy food.’

- Hippocrates 460 BC

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Diets

- Standard American Diet (SAD)
- Mediterranean
- Paleo/Ai-Paleo (no night shades)
- South Beach
- Atkins
- Vegetarian
- Vegan
- Intermittent fasting
- Cleanses
- Juicing
- FODMAPS
- Raw foods
- Gluten-free
- Anti-Inflammatory Diet

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Arthritis Care & Research

American College of Rheumatology

Brief Report

Diet and Rheumatoid Arthritis Symptoms: Survey Results From a Rheumatoid Arthritis Registry

Sara K. Tedeschi, Michelle Frits, Jing Cui, Zhi Zack Zhang, Taysir Mahmoud, Christine Iannaccone, Tzu-Chieh Lin, Kazuki Yoshida, ... See all authors

First published: 19 February 2017 | https://doi.org/10.1002/acr.23225 | Cited by: 4

The Brigham Rheumatoid Arthritis Sequential Study registry is funded by Amgen, Bristol-Myers Squibb, Crescendo Biosciences, DxTerity, and UCB.
Drs. Tedeschi and Solomon's work was supported by the NIH (grants L30-AR-070514 and K24-AR-055989, respectively).
Drs. Weinblatt and Shadick receive salary support from research grants to their institution from Amgen, Bristol-Myers Squibb, Crescendo Biosciences, DxTerity, and UCB. Dr. Solomon receives salary support from research grants to his institution from Amgen, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, Genentech, and Pfizer.

CONCLUSION:
Nearly one-quarter of RA subjects with longstanding disease reported that diet had an effect on their RA symptoms.

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REVIEW ARTICLE

Role of Diet in Influencing Rheumatoid Arthritis Disease Activity

Humeira Badsha*

Dr. Humeira Badsha Medical Center, Beach Park Plaza, Jumeira Road, Dubai, UAE

Received: December 16, 2017 Revised: January 6, 2018 Accepted: January 21, 2018

Abstract:

Background:

Patients with Rheumatoid Arthritis (RA) frequently ask their doctors about which diets to follow, and even in the absence of advice from their physicians, many patients are undertaking various dietary interventions.

Discussion:

However, the role of dietary modifications in RA is not well understood. Several studies have tried to address these gaps in our understanding. Intestinal microbial modifications are being studied for the prevention and management of RA. Some benefits of vegan diet may be explained by antioxidant constituents, lactobacilli and fibre, and by potential changes in intestinal flora. Similarly, Mediterranean diet shows anti-inflammatory effects due to protective properties of omega-3 polyunsaturated fatty acids and vitamins, but also by influencing the gut microbiome. Gluten-free and elemental diets have been associated with some benefits in RA though the existing evidence is limited. Long-term intake of fish and other sources of long-chain polyunsaturated fatty acids are protective for development of RA. The benefits of fasting, anti-oxidant supplementation, flavanoids, and probiotics in RA are not clear. Vitamin D has been shown to influence autoimmunity and specifically decrease RA disease activity. The role of supplements such as fish oils and vitamin D should be explored in future trials to gain new insights in disease pathogenesis and develop RA-specific dietary recommendations.

Conclusion:

Specifically more research is needed to explore the association of diet and the gut microbiome and how this can influence RA disease activity.

Keywords: Diet, Rheumatoid arthritis, Microbiome, Inflammation, Dysbiosis, Disease

Mediterranean diet shows anti-inflammatory effects due to protective properties of omega-3 polyunsaturated fatty acids and vitamins, but also by influencing the gut microbiome.

Mediterranean Diet

- Whole fruits & grains, legumes, nuts, seeds, low-fat dairy, wine, olive oil (fewer pesticides!)
- Extra virgin olive oil: reductions in CRP
- Walnuts: reductions in Total complement, LDL, TGs, ApoB, IL-B, TNF-alpha, VCAM-1 and CRP
- Red wine: increase in HDL-C, decrease in NFk-beta, hs-CRP, IL-6, VCAM-1
- Fiber: decrease hs-CRP, IL-6, TNF-alpha
- Flax seed: decrease total complement, LDL-C, Lp(a), TNF-alpha, sICAM, platelets aggregation (not CRP)
- Adherence was associated with signif. decrease in all cause mortality and chronic disease (CA, depression, risk for Parkinson's, Alzheimer's mobility in the elderly, CAD.)

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Arthritis Care & Research
Vol. 70, No. 3, March 2018, pp 327–332
DOI 10.1002/acr.23295

ORIGINAL ARTICLE

Relationship Between Fish Consumption and Disease Activity in Rheumatoid Arthritis

SARA K. TEDESCHI,[1] JOAN M. BATHON,[2] JON T. GILES,[2] TZU-CHIEH LIN,[1] KAZUKI YOSHIDA,[3] AND DANIEL H. SOLOMON[1]

Objective. To assess whether more frequent fish consumption is associated with lower rheumatoid arthritis (RA) disease activity scores among participants in an RA cohort.

Methods. We conducted a cross-sectional analysis using baseline data from participants in the Evaluation of Subclinical Cardiovascular Disease and Predictors of Events in Rheumatoid Arthritis cohort study. Frequency of fish consumption was assessed by a baseline food frequency questionnaire assessing usual diet in the past year. Multivariable, total energy–adjusted linear regression models provided effect estimates and 95% confidence intervals (95% CIs) for frequency of fish consumption (i.e., never to <1 time/month, 1 time/month to <1 time/week, 1 time/week, and ≥2 times/week) on baseline Disease Activity Score in 28 joints (DAS28) using the C-reactive protein (CRP) level. We also estimated the difference in DAS28-CRP associated with increasing fish consumption by 1 serving per week.

Results. Among 176 participants, the median DAS28-CRP score was 3.5 (interquartile range 2.9–4.3). In an adjusted linear regression model, subjects consuming fish ≥2 times/week had a significantly lower DAS28-CRP compared with subjects who ate fish never to <1 time/month (difference −0.49 [95% CI −0.97, −0.02]). For each additional serving of fish per week, DAS28-CRP was significantly reduced by 0.18 (95% CI −0.35, −0.004).

Conclusion. Our findings suggest that higher intake of fish may be associated with lower disease activity in RA patients.

Conclusion: study suggests, higher intake of fish may be associated with lower disease activity in RA patients.

Diet

- Oils
  - Omega-3 fish oil or flax seed oil
  - Extra virgin olive oil
- Spices
  - Garlic
  - Ginger
  - Tumeric/curcumin
  - Curry
  - Cloves
- Antioxidants
  - Vitamin D,C,E
  - Green tea (EGCG)

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Gut Microbiome

- Links to pathogenesis of RA with Prevotella copri in gut
- RA links to the oral bacterium: Aggregatibacter actinomycetemcomitans (Aa)
- P. faecalis in the oral microbiome for RA
- Provetella histicola: suppresses inflammatory arthritis in humanized mice
- Lowered faecalibacterium in Crohn's Disease
- Decreased levels of commensal Clostridia (a class of Firmicutes established early infancy and important for gut homeostasis) with scleroderma
- Netherlands study 2017 for OA:
  - two families from the Clostridiales order…associated with hip WOMAC and Kellgren-Lawrence scores
  - Knee OA was associated with Streptococcus (G+)
  - Hypothesis: Strep can cause vesicles that move from gut into bloodstream, activate immune system …macrophages through TLR4 receptors…cause low-grade systemic and localized inflammation

Still too early…..but it's coming!!!

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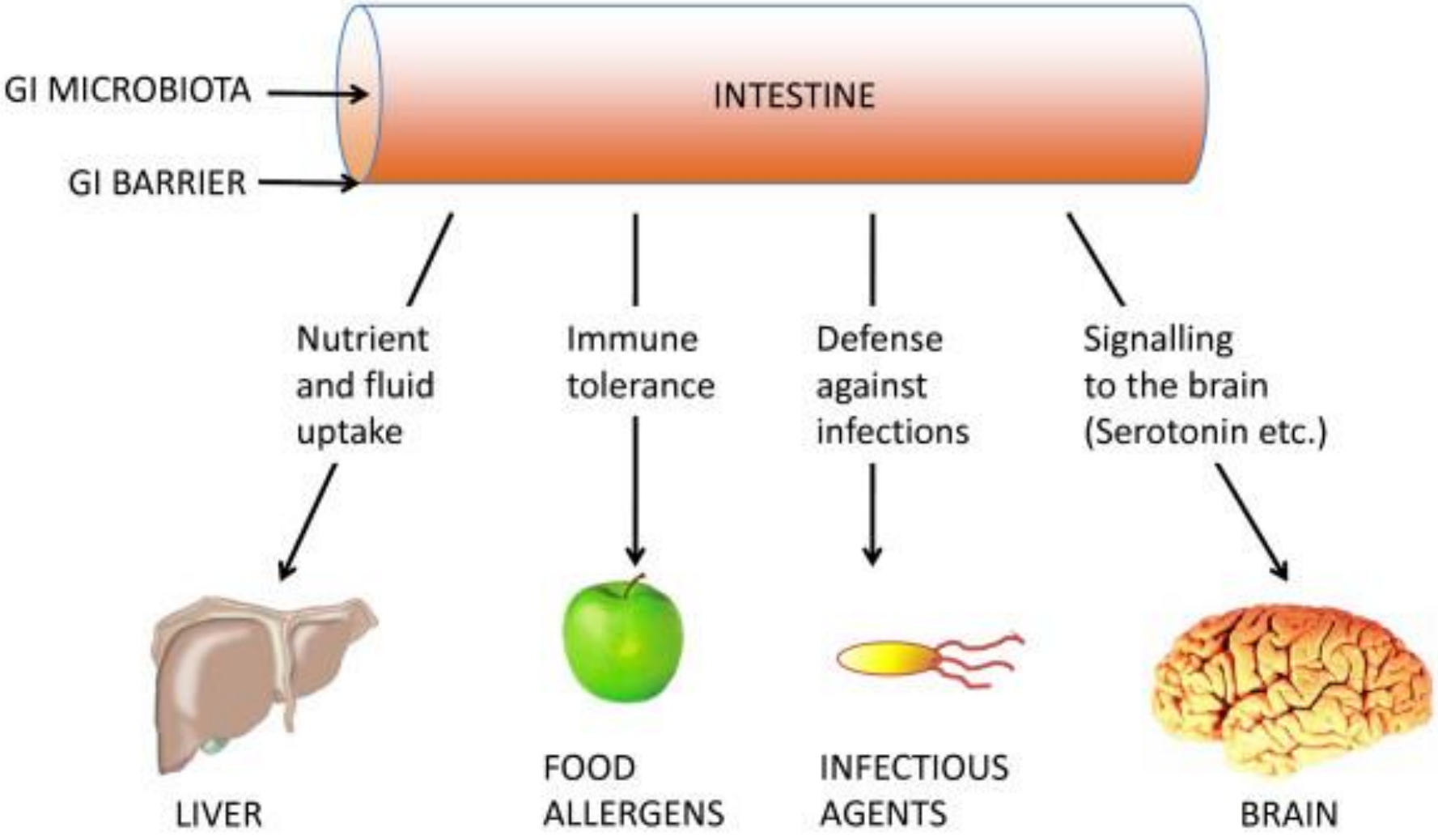

IMMUNOLOGY REVIEW ARTICLE

Intestinal dysbiosis and probiotic applications in autoimmune diseases

Gislane Lelis Vilela de Oliveira,[1] Aline Zazeri Leite,[1] Bruna Stevanato Higuchi,[1] Marina Ignácio Gonzaga[1,2] and Vânia Sammartino Mariano[2]

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doi:10.1111/imm.12765
Received 24 February 2017; revised 19 May 2017; accepted 24 May 2017.
Correspondence: Gislane Lelis Vilela de Oliveira, Faculdade de Ciências da Saúde Dr Paulo Prata (FACISB), Avenida Loja Maçônica Renovadora 68, no. 100, 14075-002, Barretos, São Paulo, Brazil. Email:

Summary

In humans, a complex interaction between the host immune system and commensal microbiota is required to maintain gut homeostasis. In this symbiotic relationship, the microbiota provides carbohydrate fermentation and digestion, vitamin synthesis and gut-associated lymphoid tissue development, as well as preventing colonization by pathobionts, whereas the host offers a niche and nutrients for the survival of the microbiota. However, when this mutualistic relationship is compromised and an altered interaction between immune cells and microorganisms occurs, the gut microbiota may cause or contribute to the establishment of infectious diseases and trigger autoimmune diseases. Researchers have made efforts to clarify the role of the microbiota in autoimmune disease development and find new therapeutic approaches to treat immune-mediated diseases. However, the exact mechanisms involved in the dysbiosis and breakdown of the gut epithelial barrier are currently unknown. Here, we provide a general overview of studies describing gut microbiota perturbations in animal models of autoimmune diseases, such as type 1 diabetes, multiple sclerosis, rheumatoid arthritis and systemic lupus erythematosus. Moreover, we include the main studies concerning dysbiosis in humans and a critical discussion of the existing data on the use of probiotics in these autoimmune diseases.

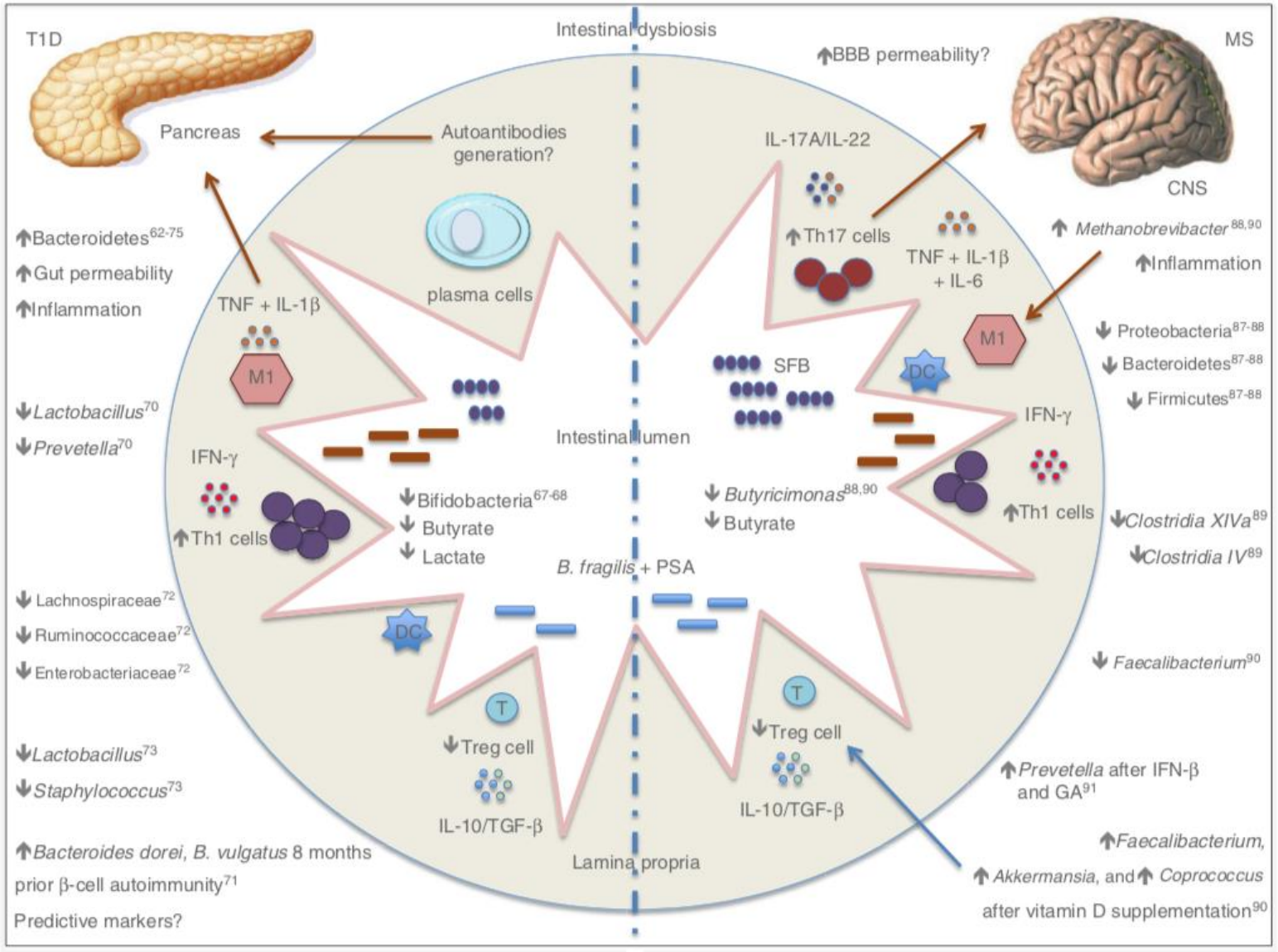

Figure 2. A schematic representation of the intestinal dysbiosis in organ-specific autoimmune diseases in humans.

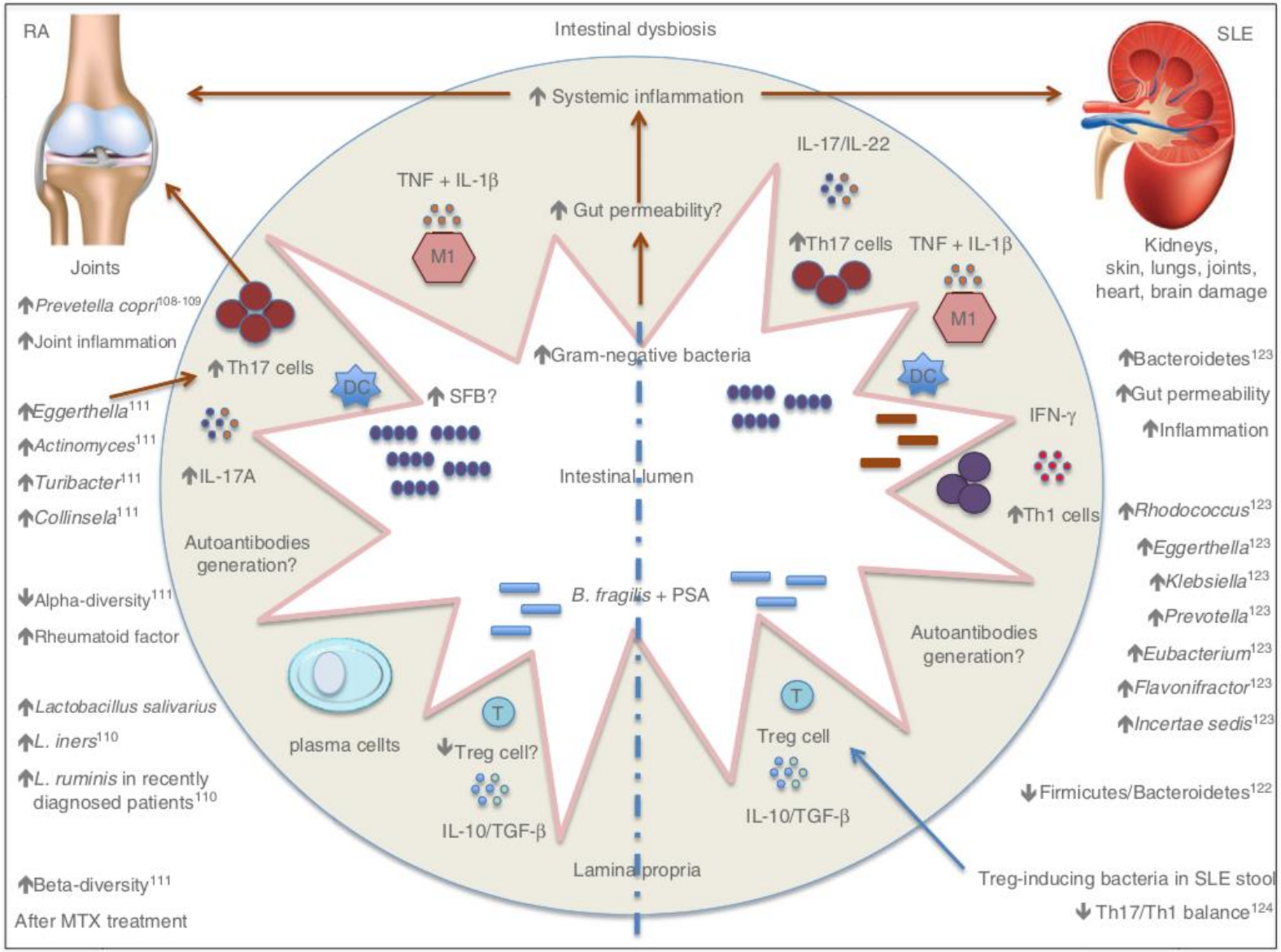

Figure 3. A schematic representation of intestinal dysbiosis in rheumatic autoimmune diseases in humans.

Environmental factors dominate over host genetics in shaping human gut microbiota composition

Daphna Rothschild[1,2,9], Omer Weissbrod[1,2,9], Elad Barkan[1,2,9], Tal Korem[1,2], David Zeevi[1,2], Paul I Costea[1,2], Anastasia Godneva[1,2], Iris Kalka[1,2], Noam Bar[1,2], Niv Zmora[3,4,5], Meirav Pevsner-Fischer[3], David Israeli[6], Noa Kosower[1,2], Gal Malka[1,2], Bat Chen Wolf[1,2], Tali Avnit-Sagi[1,2], Maya Lotan-Pompan[1,2], Adina Weinberger[1,2], Zamir Halpern[5,7], Shai Carmi[8], Eran Elinav[3*] and Eran Segal[1,2*]

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…environment "trumps" genetics with gut microbiome composition
Overall, our results suggest that human microbiome composition is dominated by environmental factors rather than by host genetics.

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Nature, 2018

Extensive impact of non-antibiotic drugs on human gut bacteria

Lisa Maier[1]*, Mihaela Pruteanu[1]†*, Michael Kuhn[2]*, Georg Zeller[2], Anja Telzerow[1], Exene Erin Anderson[1], Ana Rita Brochado[1], Keith Conrad Fernandez[1], Hitomi Dose[3], Hirotada Mori[3], Kiran Raosaheb Patil[2], Peer Bork[2,4,5,6] & Athanasios Typas[1,2]

A few commonly used non-antibiotic drugs have recently been associated with changes in gut microbiome composition, but the extent of this phenomenon is unknown. Here, we screened more than 1,000 marketed drugs against 40 representative gut bacterial strains, and found that 24% of the drugs with human targets, including members of all therapeutic classes, inhibited the growth of at least one strain *in vitro*. Particular classes, such as the chemically diverse antipsychotics, were overrepresented in this group. The effects of human-targeted drugs on gut bacteria are reflected on their antibiotic-like side effects in humans and are concordant with existing human cohort studies. Susceptibility to antibiotics and human-targeted drugs correlates across bacterial species, suggesting common resistance mechanisms, which we verified for some drugs. The potential risk of non-antibiotics promoting antibiotic resistance warrants further exploration. Our results provide a resource for future research on drug–microbiome interactions, opening new paths for side effect control and drug repurposing, and broadening our view of antibiotic resistance.

Pharmaceutical agents have both beneficial and undesirable effects. Studies on the mechanisms of action and off-target spectra of various drugs aim to improve their efficacy and reduce their side effects. Although many drugs have gastrointestinal side effects and the gut microbiome itself is pivotal for human health[1], the role of the gut microbiota in these processes is rarely considered. Recently, consumption of drugs designed to target human cells and not microbes, such as anti-

All compounds were screened at 20 μM, which is within the range of what is commonly used in high-throughput drug screens[9].

For our screen to be representative of the gut microbiome of healthy individuals, we selected a set of ubiquitous gut bacterial species (Supplementary Table 2). Prevalence and abundance in the human gut, and phylogenetic diversity, were our main selection criteria (Extended Data Fig. 1b), although we were occasionally constrained by strain una-

total, we included 40
l genera (*Escherichia*

24% of these human targeted pharmaceuticals inhibited growth of at least one important gut bacterial species…Study also implies an increasing risk of acquiring antibiotic resistance by being exposed to *non*-antibiotic drugs

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Probiotic Basics

Foods/Drinks

- Kimchi, sauerkraut, kombucha, low sugar Greek yogurt e.g.

Supplements

- Choose a reputable brand
- Go with diversity…with lots of different bacteria on the ingredients label
- Not all good probiotic supplements need to be refrigerated!
- Consider switching out probiotics every 6 to 12 months to create more diversity

Prebiotics

- They feed the "zoo"!
- Fermented foods: apple cider vinegar, balsamic, pickles, sauerkraut, kimchi!

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Supplements

Natural Product Dietary Supplement Use by Individuals with Rheumatoid Arthritis: A Scoping Review

Janel C DeSalvo, MD[1], Meghan B Skiba, MS[1,2], Carol L Howe, MD, MLS[3], Karen E Haiber, MD[1], Janet L Funk, MD[1]

[1]Department of Medicine, College of Medicine, University of Arizona, Tucson Arizona
[2] Department of Health Promotion Sciences, College of Public Health, University of Arizona, Tucson, Arizona
[3] University of Arizona Health Sciences Library, Tucson Arizona

Nutriceuticals

- Not regulated by FDA (in the U.S.)
  - ?compound amount
  - ?purity
  - ?long-term safety
  - ?product labeling
  - ?synergistic effects with Rx and other supplements
  - Too much of a good thing…patient overuse
  - Not covered by most insurance companies
  - Shipping methods

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Anti-inflammatory Supplements

- Ginger
- Curcumen/turmeric +/- BP
- Omega-3 fish oil
- Gammalinoleic acid (GLA)
- Cat's Claw
- Boswellia
- Ashwagandha
- S-adenosylmethionone (SAMe)
- Concentrated ginger extract
- Avocado-soybean unsaponofiables (ASUs)
- Rosa canina (rosehip)
- Curcuma domestica - +/- piperine or bioperine (black pepper)
- MCP-Modified citrus pectin
- Bomelain: pineapple enzyme
- Antioxidants: tart cherry juice, quercitin
- MSM: methyl sulfonyl methane

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Curcumin

- Active component of the common spice turmeric (4-6%)
- Exerts a wide spectrum of biological activities by modulating several transcription factors and signaling pathways
- Exhibits anti-oxidant activity
- Chemoprotective and anticancer agent
  - Inhibits cell proliferation, induces apoptosis, and growth arrest in different phases of the cell cycle, inhibits angiogenesis
- Potent anti-inflammatory substance
  - Inhibits all mediators of the inflammatory response
    - Inhibits NF-kB pathway (proinflammatory signaling pathway-"master switch")
    - Inhibits COX-2, AP-1, Egr-1, STAT
    - Reduces TNF-alpha
    - Inhibits matrix metalloproteinases

PHYTOTHERAPY RESEARCH
Phytother. Res. (2012)
Published online in Wiley Online Library
(wileyonlinelibrary.com) **DOI**: 10.1002/ptr.4639

A Randomized, Pilot Study to Assess the Efficacy and Safety of Curcumin in Patients with Active Rheumatoid Arthritis

Binu Chandran[1] and Ajay Goel[2]*
[1]Nirmala Medical Centre, Muvattupuzha, Kerala, India
[2]Baylor Research Institute and Sammons Cancer Center, Baylor University Medical Center, Dallas, TX, USA

Curcumin is known to possess potent antiinflammatory and antiarthritic properties. This pilot clinical study evaluated the safety and effectiveness of curcumin alone, and in combination with diclofenac sodium in patients with active rheumatoid arthritis (RA). Forty-five patients diagnosed with RA were randomized into three groups with patients receiving curcumin (500 mg) and diclofenac sodium (50 mg) alone or their combination. The primary endpoints were reduction in Disease Activity Score (DAS) 28. The secondary endpoints included American College of Rheumatology (ACR) criteria for reduction in tenderness and swelling of joint scores. Patients in all three treatment groups showed statistically significant changes in their DAS scores. Interestingly, the curcumin group showed the highest percentage of improvement in overall DAS and ACR scores (ACR 20, 50 and 70) and these scores were significantly better than the patients in the diclofenac sodium group. More importantly, curcumin treatment was found to be safe and did not relate with any adverse events. Our study provides the first evidence for the safety and superiority of curcumin treatment in patients with active RA, and highlights the need for future large-scale trials to validate these findings in patients with RA and other arthritic conditions.

Keywords: curcumin; diclofenac sodium; Disease Activity Score; American College of Rheumatology criteria.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflam-

Pharmacotherapy for rheumatoid arthritis generally involves treatment regimens including non-steroidal antiinflammatory drugs (NSAIDs) for the pain management, low-dose therapy using oral or intraarticular

Curcumin showed the highest percentage of improvement in overall DAS and ACR scores (20, 50, and 70) and these scores were significantly better than the patients in the diclofenac sodium group.

British Journal of Pharmacology

British Journal of Pharmacology (2017) **174** 1325–1348 1325

Themed Section: Principles of Pharmacological Research of Nutraceuticals

REVIEW ARTICLE

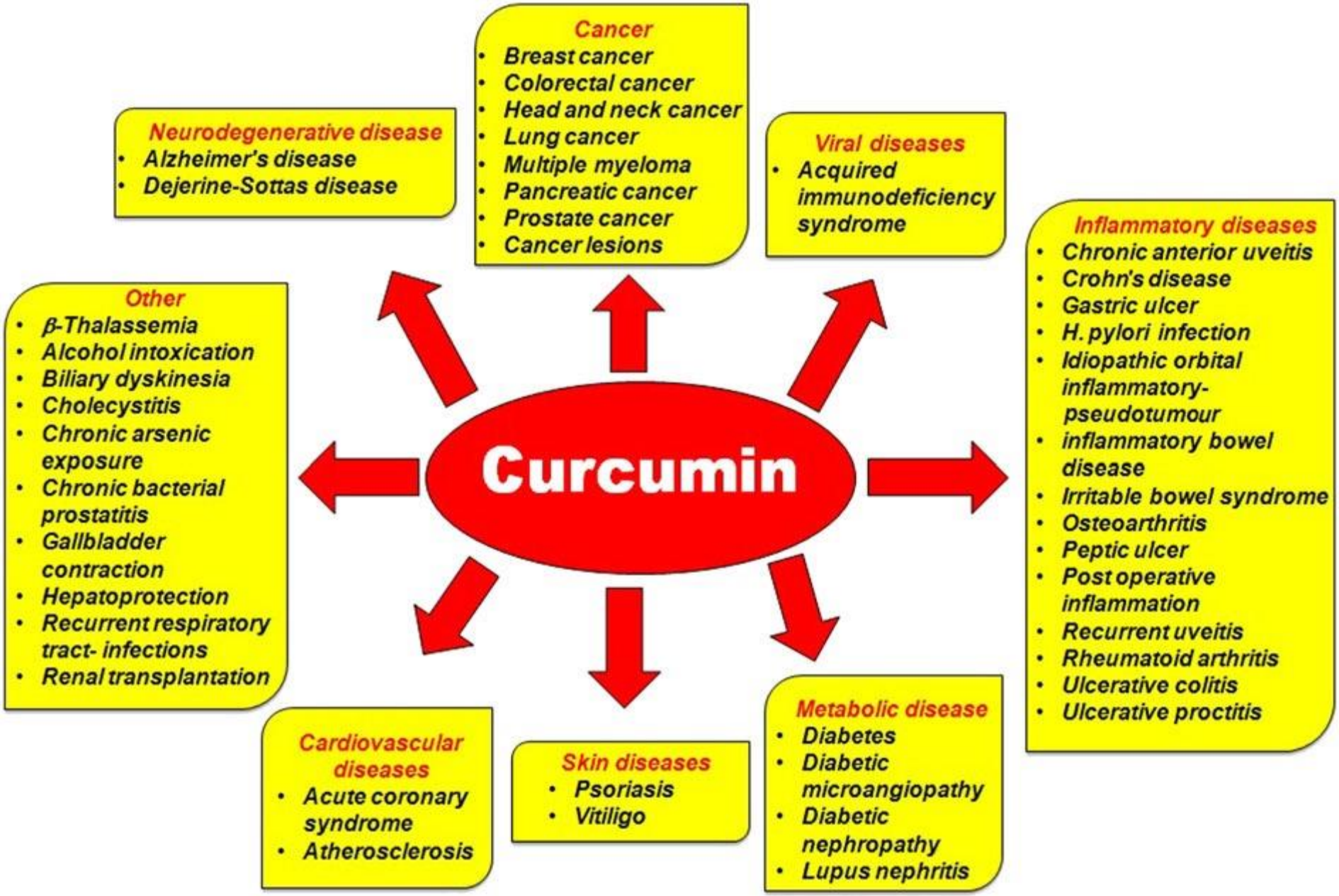
Curcumin, the golden nutraceutical: multitargeting for multiple chronic diseases

Correspondence Bharat B Aggarwal, Anti-Inflammation Research Institute, San Diego, California, USA, and Ajaikumar B Kunnumakkara, Department of Biosciences and Bioengineering, Indian Institute of Technology Guwahati, Assam, India. E-mail: bbaggarwal@gmail.com; kunnumakkara@iitg.ernet.in

Received 30 April 2016; **Revised** 15 August 2016; **Accepted** 18 August 2016

Ajaikumar B Kunnumakkara[1], Devivasha Bordoloi[1], Ganesan Padmavathi[1], Javadi Monisha[1], Nand Kishor Roy[1], Sahdeo Prasad[2] and Bharat B Aggarwal[3]

[1]Department of Biosciences and Bioengineering, Indian Institute of Technology Guwahati, Assam, India, [2]Department of Experimental Therapeutics, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA, and [3]Anti-Inflammation Research Institute, San Diego, California, USA



Alpha-Omega-3

- Anti-inflammatory agent: Alzheimer's, Parkinson's, CVD, PSA, IBD,
  - Suppresses leukotriene production, arachidonic acid, prostaglandins, thromboxane (pro-inflammatory cascade)
  - EPA: eicosapentaenoic acid
  - DHA: docosahexaenoic acid
- Used with schizophrenia, mood disorders, sleep
- "Blood thinner"- lowers risk of developing CAD and MI
- Lowers homocysteine and triglyceride levels
- Eye health: lowers risk for macular degeneration
- Arthritis benefits may be delayed by 3-4 months
- Check EPA and DHA content
- Check brands/purity/shipping… it matters!
- <u>Contraindications</u>: patients with bleeding disorders, Hx of hemorrhagic stroke, Hx of GI bleed

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ORIGINAL ARTICLE

Omega-3 Polyunsaturated Fatty Acids and the Treatment of Rheumatoid Arthritis: A Meta-analysis

Young-Ho Lee,[a] Sang-Cheol Bae,[b] and Gwan-Gyu Song[a]

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Received for publication February 14, 2012; accepted June 6, 2012 (ARCMED-D-12-00081).

Background and Aims. We undertook this study to assess the effects of omega-3 polyunsaturated fatty acids (PUFAs) (administered at ≥2.7 g/day) for a minimum duration of 3 months on clinical outcomes in patients with rheumatoid arthritis (RA).

Methods. The authors surveyed randomized controlled trials (RCTs) that examined the effects of omega-3 PUFAs on clinical outcomes in RA patients using Medline and the Cochrane Controlled Trials Register and by performing manual searches. Meta-analysis of RCTs was performed using fixed and random effects models. Outcomes are presented as standardized mean differences (SMD).

Results. Ten RCTs involving 183 RA patients and 187 placebo-treated RA controls were included in this meta-analysis. The analysis showed that omega-3 PUFAs clearly reduced nonsteroidal anti-inflammatory drug (NSAID) consumption (SMD −0.518, 95% CI −0.915 to −0.121, $p = 0.011$) without between-study heterogeneity ($I^2 = 0\%$). Tender joint count (SMD −0.214, 95% CI−0.489−0.062, $p = 0.128$), swollen joint count (SMD −0.170, 95% CI−0.454−0.114, $p = 0.241$), morning stiffness (SMD −0.224, 95% CI−0.955−0.212, $p = 0.221$), and physical function (SMD 0.264, 95% CI−0.232−0.724, $p = 0.314$) showed a trend to improve more in patients treated with omega-3 PUFAs than in placebo-treated controls, but they did not reach statistical significance.

Conclusions. This meta-analysis suggests that the use of omega-3 PUFAs at dosages >2.7 g/day for >3 months reduces NSAID consumption by RA patients. Further studies are needed to explore the clinical and NSAID-sparing effects of omega-3 PUFAs in RA.

Conclusions: This meta-analysis suggests that the use of omega-3 PUFAs at dosages >2.7 g/day for >3 months reduces NSAID consumption by RA patients.

Other Important Nutrients

- Vitamin D (RA, SLE, MS, CAD, vasculitis, energy)
- Vitamin C (gout, RSD, sepsis)
- Magnesium (pain control, HTN, migraines)
- Medium chain triglycerides (MCT) (Alzheimer's, vasculitis, RA)
- Iron (anemia of chronic disease vs. acute loss)
- Pre/synbiotics

Air Quality

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RMD Open
Rheumatic & Musculoskeletal Diseases

ORIGINAL RESEARCH

Association between long-term exposure to air pollution and immune-mediated diseases: a population-based cohort study

Giovanni Adami ,[1] Marco Pontalti,[1] Giorgio Cattani,[2] Maurizio Rossini,[1] Ombretta Viapiana,[1] Giovanni Orsolini ,[1] Camilla Benini,[1] Eugenia Bertoldo,[1] Elena Fracassi,[1] Davide Gatti,[1] Angelo Fassio[1]

Conclusion: Long-term exposure to air pollution was associated with higher risk of developing autoimmune diseases, in particular rheumatoid arthritis, CTDs and IBD. Chronic exposure to levels above the threshold for human protection was associated with a 10% higher risk of developing IMIDs.

Adami G, Pontalti M, Cattani G, et al. Association between long-term exposure to air pollution and immune-mediated diseases: a population-based cohort study. RMD Open 2022;**8**:e002055. doi:10.1136/ rmdopen-2021-002055

Environmental Science & Technology

Article

pubs.acs.org/est

Consumer Product Chemicals in Indoor Dust: A Quantitative Meta-analysis of U.S. Studies

Susanna D. Mitro,[†] Robin E. Dodson,[‡] Veena Singla,[§] Gary Adamkiewicz,[∥] Angelo F. Elmi,[†] Monica K. Tilly,[§,⊥] and Ami R. Zota*[,†]

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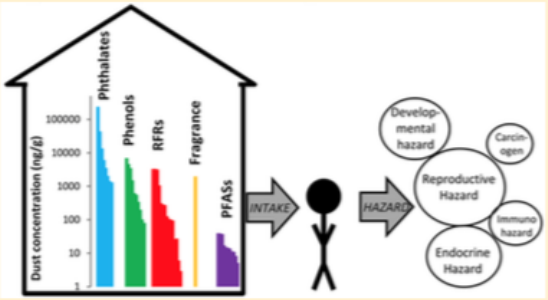
Supporting Information

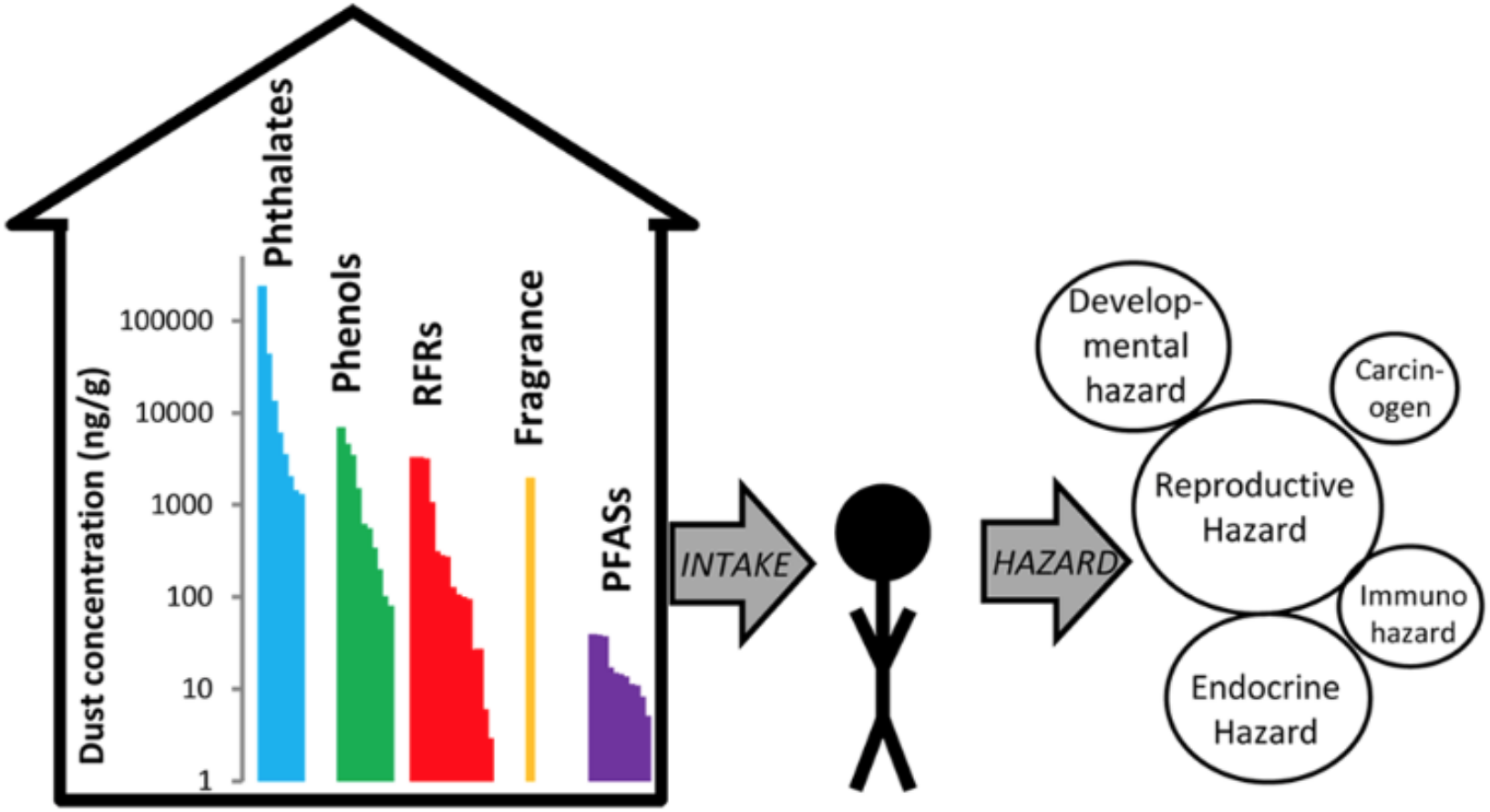
ABSTRACT: Indoor dust is a reservoir for commercial consumer product chemicals, including many compounds with known or suspected health effects. However, most dust exposure studies measure few chemicals in small samples. We systematically searched the U.S. indoor dust literature on phthalates, replacement flame retardants (RFRs), perfluoroalkyl substances (PFASs), synthetic fragrances, and environmental phenols and estimated pooled geometric means (GMs) and 95% confidence intervals for 45 chemicals measured in ≥3 data sets. In order to rank and contextualize these results, we used the pooled GMs to calculate residential intake from dust ingestion, inhalation, and dermal uptake from air, and then identified hazard traits from the Safer Consumer Products Candidate Chemical List. Our results indicate that U.S. indoor dust consistently contains chemicals from multiple classes. Phthalates occurred in the highest concentrations, followed by phenols, RFRs, fragrance, and PFASs. Several phthalates and RFRs had the highest residential intakes. We also found that many chemicals in dust share hazard traits such as reproductive and endocrine toxicity. We offer recommendations to maximize comparability of studies and advance indoor exposure science. This information is critical in shaping future exposure and health studies, especially related to cumulative exposures, and in providing evidence for intervention development and public policy.



INTRODUCTION

People in developed countries spend more than 90% of their time in indoor environments,[1] creating an important link between indoor environmental quality and public health. Consumer products and building materials including furniture, electronics, personal care and cleaning products, and floor and wall coverings contain chemicals that can leach, migrate, abrade, or off-gas from products resulting in human exposure.[2,3] Consequently, chemicals such as phthalates, phenols, flame retardants, and polyfluorinated alkyl substances (PFASs) are

exist in the gas and condensed phase and redistribute from their original source over time, partitioning between indoor air, dust, and surfaces. Consequently, exposure to SVOC chemicals in the indoor environment may occur from air, dust, and dermal pathways.[10−13] For some phthalate diesters, the use of consumer products and indoor exposures are major contributors to human exposure.[14−17] Similarly, for some flame retardants, dust is a significant contributor to exposure,[18−20] while the contribution of the indoor environment to total exposure of PFASs is less well characterized.[21,22] The chemical properties, sources, exposure



…..we also found that many chemicals in dust share hazard traits such as reproductive and endocrine toxicity.

Mitro, S.D., et al. 2016. Consumer Product Chemicals in Indoor Dust: A Quantitative Meta-analysis of U.S. Studies. *Environmental science & technology*

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Published in final edited form as:
J Environ Monit. 2009 January ; 11(1): 205–211. doi:10.1039/b807821a.

Evaluation of HEPA vacuum cleaning and dry steam cleaning in reducing levels of polycyclic aromatic hydrocarbons and house dust mite allergens in carpets

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[b]Department of Public Health, Tzu-Chi University, Hualien, 97004, Taiwan ROC

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Abstract

Dry steam cleaning, which has gained recent attention as an effective method to reduce house dust mite (HDM) allergen concentration and loading in carpets, was evaluated in this study for its efficacy in lowering levels of polycyclic aromatic hydrocarbons (PAHs) as well as HDM allergens. Fifty urban homes with wail-to-wall carpets, mostly low-income and with known lead contamination, were studied in 2003 and 2004. Two carpet-cleaning interventions were compared: Repeated HEPA (High Efficiency Particulate Air filtered) vacuuming alone and repeated HEPA vacuuming supplemented with dry steam cleaning. Vacuum samples were collected to measure carpet loading of dust and contaminants immediately before and after cleaning. Paired

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Results of a Home-Based Environmental Intervention among Urban Children with Asthma

Wayne J. Morgan, M.D., C.M., Ellen F. Crain, M.D., Ph.D., Rebecca S. Gruchalla, M.D., Ph.D., George T. O'Connor, M.D., Meyer Kattan, M.D., C.M., Richard Evans III, M.D., M.P.H., James Stout, M.D., M.P.H., George Malindzak, Ph.D., Ernestine Smartt, R.N., Marshall Plaut, M.D., Michelle Walter, M.S., Benjamin Vaughn, M.S., and Herman Mitchell, Ph.D., for the Inner-City Asthma Study Group*

ABSTRACT

BACKGROUND

Children with asthma who live in the inner city are exposed to multiple indoor allergens and environmental tobacco smoke in their homes. Reductions in these triggers of asthma have been difficult to achieve and have seldom been associated with decreased morbidity from asthma. The objective of this study was to determine whether an environmental intervention tailored to each child's allergic sensitization and environmental risk factors could improve asthma-related outcomes.

METHODS

We enrolled 937 children with atopic asthma (age, 5 to 11 years) in seven major U.S. cities in a randomized, controlled trial of an environmental intervention that lasted one year (intervention year) and included education and remediation for exposure to both allergens and environmental tobacco smoke. Home environmental exposures were assessed every six months, and asthma-related complications were assessed every two months during the intervention and for one year after the intervention.

RESULTS

For every 2-week period, the intervention group had fewer days with symptoms than did the control group both during the intervention year (3.39 vs. 4.20 days, $P<0.001$) and the year afterward (2.62 vs. 3.21 days, $P<0.001$), as well as greater declines in the

Pesticides

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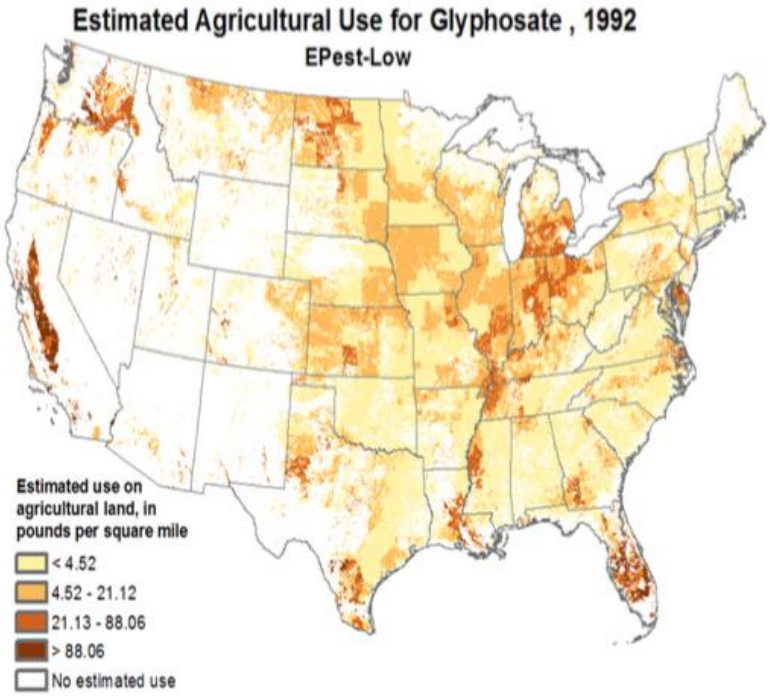
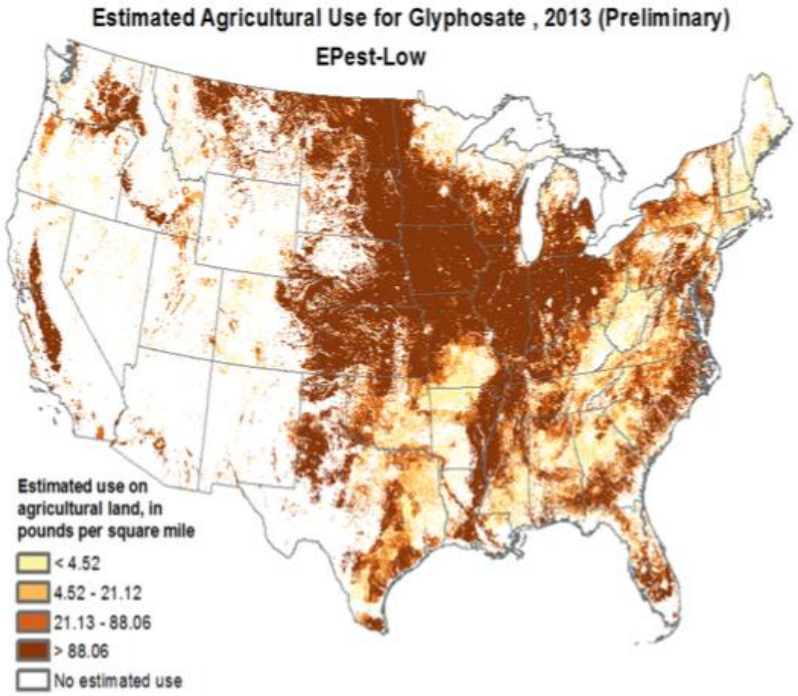
Glyphosate usage in the U.S.





USGS Pesticide National Synthesis Project

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Residential Exposure to Pesticide During Childhood and Childhood Cancers: A Meta-Analysis

Mei Chen, PhD, MS, Chi-Hsuan Chang, MSc, Lin Tao, PhD, Chensheng Lu, PhD, MS

abstract

CONTEXT: There is an increasing concern about chronic low-level pesticide exposure during childhood and its influence on childhood cancers.

OBJECTIVE: In this meta-analysis, we aimed to examine associations between residential childhood pesticide exposures and childhood cancers.

DATA SOURCES: We searched all observational studies published in PubMed before February 2014 and reviewed reference sections of articles derived from searches.

STUDY SELECTION: The literature search yielded 277 studies that met inclusion criteria.

DATA EXTRACTION: Sixteen studies were included in the meta-analysis. We calculated effect sizes and 95% confidence intervals (CIs) by using a random effect model with inverse variance weights.

RESULTS: We found that childhood exposure to indoor but not outdoor residential insecticides was associated with a significant increase in risk of childhood leukemia (odds ratio [OR] = 1.47; 95% CI, 1.26–1.72; I^2 = 30%) and childhood lymphomas (OR = 1.43; 95% CI, 1.15–1.78; I^2 = 0%). A significant increase in risk of leukemia was also associated with herbicide exposure (OR = 1.26; 95% CI, 1.10–1.44; I^2 = 0%). Also observed was a positive but not statistically significant association between childhood home pesticide or herbicide exposure and childhood brain tumors.

LIMITATIONS: The small number of studies included in the analysis represents a major limitation of the current analysis.

…children exposed to indoor insecticides would have a higher risk of childhood hematopoietic cancers

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Review Article

Genetic Profile, Environmental Exposure, and Their Interaction in Parkinson's Disease

Letizia Polito,[1] Antonio Greco,[2] and Davide Seripa[2]

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[2] *Geriatric Unit and Gerontology-Geriatrics Research Laboratory, Department of Medical Sciences, IRCCS Casa Sollievo della Sofferenza, San Giovanni Rotondo, 71013 Foggia, Italy*

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Received 23 October 2015; Revised 5 January 2016; Accepted 10 January 2016

Academic Editor: Jan O. Aasly

The discovery of causative mutations for Parkinson's disease (PD) as well as their functional characterization in cellular and animal models has provided crucial insight into the pathogenesis of this disorder. Today, we know that PD pathogenesis involves multiple related processes including mitochondrial dysfunction, oxidative and nitrative stress, microglial activation and inflammation, and aggregation of α-synuclein and impaired autophagy. However, with the exception of a few families with Mendelian inheritance, the cause of PD in most individuals is yet unknown and the identified genetic susceptibility factors have only small effect size. Epidemiologic studies have found increased risk of PD associated with exposure to environmental toxicants such as pesticides, organic solvents, metals, and air pollutants, while reduced risk of PD associated with smoking cigarettes and coffee consumption. The role of environmental exposure, as well as the contribution of single genetic risk factors, is still controversial. In most of PD cases, disease onset is probably triggered by a complex interplay of many genetic and nongenetic factors, each of which conveys a minor increase in the risk of disease. This review summarizes the current knowledge on causal mutation for PD, susceptibility factors increasing disease risk, and the genetic factors that modify the impact of environmental exposure.

1. Introduction

Nineteen years ago, the discovery of the first genetic mutation responsible for Parkinson's disease (PD), p.A53T in the α-synuclein (*SNCA*) gene [1], provided the initial insights into the molecular genetics of PD. This finding was followed by data showing that α-synuclein is the major component of Lewy bodies (LB), a hallmark lesion in PD and other α-synucleinopathies [2]. Since then, an intensive search for other genetic causes for PD was launched and other mutated genes were reported to cause autosomal dominant or recessive forms of PD. Although monogenic forms are rare and altogether represent less than 10% of all PD cases [3], their functional characterization in cellular and animal models provided valuable insights into PD etiologic mech- dysfunction, oxidative and nitrosative stress, microglial activation and inflammation, and aggregation of α-synuclein and impaired autophagy, derive [5]. Besides rare causative mutations, several genetic susceptibility loci were discovered but with small to modest effect sizes [6].

Exploring the contribution of environmental exposure markedly advanced our understanding of the mechanisms involved in the development of PD. Initial evidence came from findings that subjects exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) developed PD-like symptoms [7]. Since then, environmental exposure to pesticides [8, 9], polychlorinated biphenyls [10], organic solvents [11], metals [12], and air pollutants [13] has been proposed to increase risk for PD. However, results concerning the contribution of environmental factors in PD are still inconsistent

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Pesticides

- Clean floors and carpeting regularly
- Wash produce with vinegar and water or safe produce detergent
- Buy organics when possible or use EWG Dirty Dozen/Clean Fifteen
- Limit foods with high animal fat…pesticides can accumulate
- Avoid spraying of pesticides
- Avoid cleaners and personal care products that say "antimicrobial"
- Remove contaminated shoes, boots, and clothing
- Be aware of agricultural spraying near home, work, and schools
- Avoid pesticides on pets (flea and tick collars, shampoos and dips)
- Clean of pet's feet as well
- Vacuum with HEPA filter and dust regularly
- Wear personal protective equipment when gardening/farming
- Use Integrated Pest Management (IPM) alternatives

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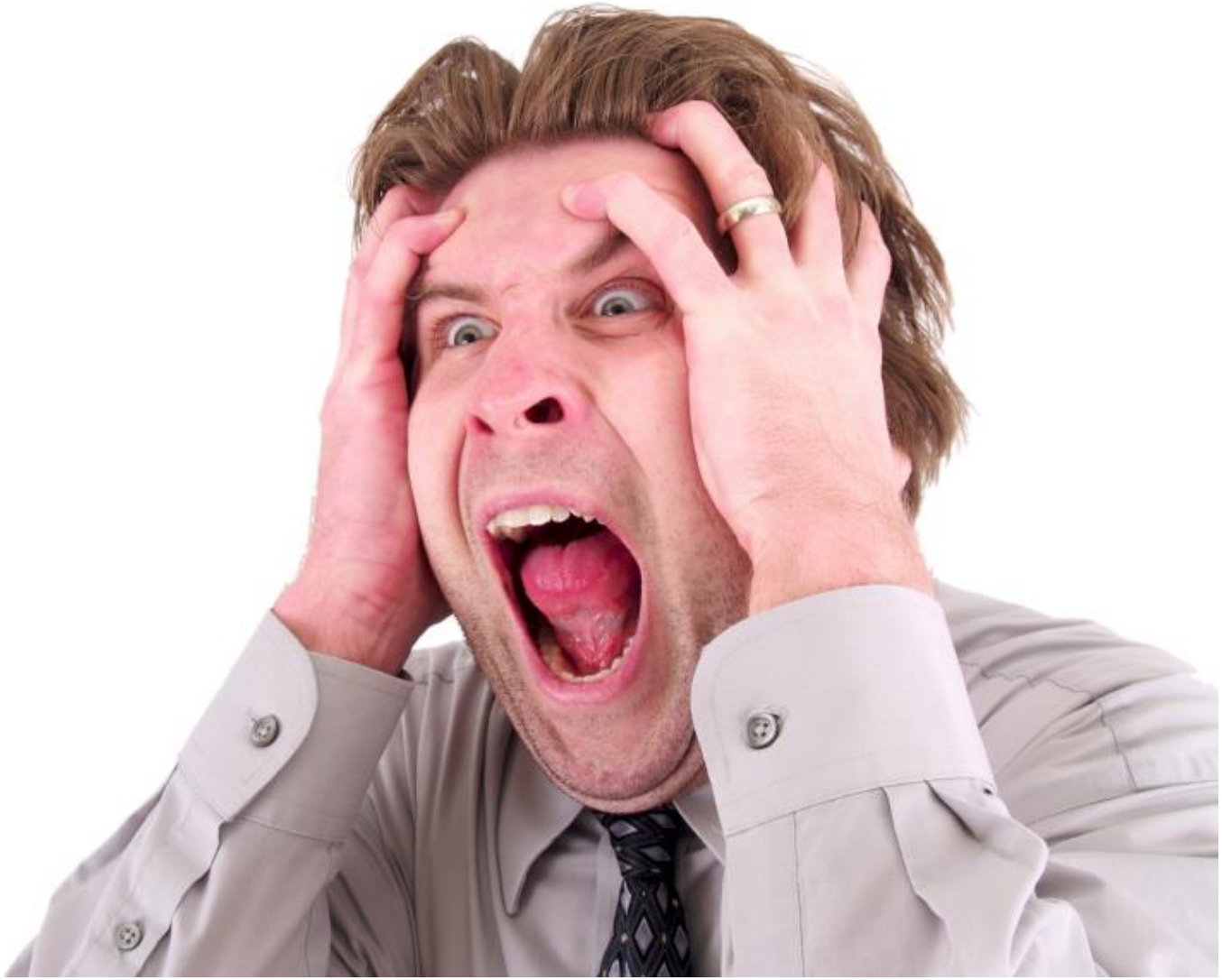
Stress



Research Article

Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults

The Adverse Childhood Experiences (ACE) Study

Vincent J. Felitti, MD, FACP, Robert F. Anda, MD, MS, Dale Nordenberg, MD, David F. Williamson, MS, PhD, Alison M. Spitz, MS, MPH, Valerie Edwards, BA, Mary P. Koss, PhD, James S. Marks, MD, MPH

Background: The relationship of health risk behavior and disease in adulthood to the breadth of exposure to childhood emotional, physical, or sexual abuse, and household dysfunction during childhood has not previously been described.

Methods: A questionnaire about adverse childhood experiences was mailed to 13,494 adults who had completed a standardized medical evaluation at a large HMO; 9,508 (70.5%) responded. Seven categories of adverse childhood experiences were studied: psychological, physical, or sexual abuse; violence against mother; or living with household members who were substance abusers, mentally ill or suicidal, or ever imprisoned. The number of categories of these adverse childhood experiences was then compared to measures of adult risk behavior, health status, and disease. Logistic regression was used to adjust for effects of demographic factors on the association between the cumulative number of categories of childhood exposures (range: 0–7) and risk factors for the leading causes of death in adult life.

Results: More than half of respondents reported at least one, and one-fourth reported ≥2 categories of childhood exposures. We found a graded relationship between the number of categories of childhood exposure and each of the adult health risk behaviors and diseases that were studied ($P < .001$). Persons who had experienced four or more

We found a strong graded relationship between the breadth of exposure to abuse or household dysfunction during childhood and multiple risk factors for several of the leading causes of death in adults.

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JAMA | Original Investigation

Association of Stress-Related Disorders With Subsequent Autoimmune Disease

Huan Song, MD, PhD; Fang Fang, MD, PhD; Gunnar Tomasson, MD, PhD; Filip K. Arnberg, PhD; David Mataix-Cols, PhD; Lorena Fernández de la Cruz, PhD; Catarina Almqvist, MD, PhD; Katja Fall, MD, PhD; Unnur A. Valdimarsdóttir, PhD

IMPORTANCE Psychiatric reactions to life stressors are common in the general population and may result in immune dysfunction. Whether such reactions contribute to the risk of autoimmune disease remains unclear.

OBJECTIVE To determine whether there is an association between stress-related disorders and subsequent autoimmune disease.

DESIGN, SETTING, AND PARTICIPANTS Population- and sibling-matched retrospective cohort study conducted in Sweden from January 1, 1981, to December 31, 2013. The cohort included 106 464 exposed patients with stress-related disorders, with 1 064 640 matched unexposed persons and 126 652 full siblings of these patients.

EXPOSURES Diagnosis of stress-related disorders, ie, posttraumatic stress disorder, acute

…exposure to a stress-related disorder was ***significantly*** associated with increased risk of subsequent autoimmune disease, compared with matched unexposed individuals and with full siblings.

Association of Exposure to Childhood Abuse with Incident Systemic Lupus Erythematosus in a Longitudinal Cohort of Women

Candace H. Feldman[1], Susan Malspeis[2], Cianna Leatherwood[1], Laura Kubzansky[3], Karen Costenbader[1] and Andrea Roberts[4], [1]Division of Rheumatology, Immunology and Allergy, Brigham and Women's Hospital, Boston, MA, [2]Brigham and Women's Hospital, Boston, MA, [3]Social and Behavioral Sciences, Harvard T.H. Chan School of Public Health, Boston, MA, [4]Harvard T.H. Chan School of Public Health, Boston, MA

Meeting: 2018 ACR/ARHP Annual Meeting

Keywords: epidemiologic methods and trauma, Lupus

SESSION INFORMATION

Date: Tuesday, October 23, 2018

Session Title: 5T086 ACR Abstract: Epidemiology & Pub Health III: SLE & SSc, Big Data & Large Cohorts (2802–2807)

Session Type: ACR Concurrent Abstract Session

Session Time: 2:30PM-4:00PM

Background/Purpose: Prior studies demonstrated associations between post-traumatic stress disorder and increased risk of incident SLE and between childhood trauma and increased risk of hospitalization for autoimmune disease during adulthood. Severe stressors may alter immune function and result in increased inflammation and cytokine release, thereby increasing risk of SLE.

Conclusion: …we observed *significantly increased* risk of incident SLE among women who experienced childhood physical and emotional abuse compared with women who had not.

and

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Ann N Y Acad Sci. 2016 June ; 1373(1): 13–24. doi:10.1111/nyas.12998.

Mindfulness meditation and the immune system: a systematic review of randomized controlled trials

David S. Black[1] and **George M. Slavich**[2]

[1]Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, California

[2]Cousins Center for Psychoneuroimmunology and Department of Psychiatry and Biobehavioral Sciences, University of California, Los Angeles, California

Abstract

Mindfulness meditation represents a mental training framework for cultivating the state of mindful awareness in daily life. Recently, there has been a surge of interest in how mindfulness meditation improves human health and well-being. Although studies have shown that mindfulness meditation can improve self-reported measures of disease symptomatology, the effect that mindfulness meditation has on biological mechanisms underlying human aging and disease is less clear. To address this issue, we conducted the first comprehensive review of randomized controlled trials examining the effects of mindfulness meditation on immune system parameters, with a specific focus on five outcomes: (1) circulating and stimulated inflammatory proteins, (2) cellular transcription factors and gene expression, (3) immune cell count, (4) immune cell aging, and (5) antibody response. This analysis revealed substantial heterogeneity across studies with respect to patient population, study design, and assay procedures. The findings suggest possible effects of mindfulness meditation on specific markers of inflammation, cell-mediated immunity, and biological aging, but these results are tentative and require further replication. On the basis of this

….mindfulness mediation appears to be associated with reductions in proinflammatory processes, increases in cell-mediated defense parameters, and increases in enzyme activity that guards against cell aging.

Other Measures

- Stress management
- Sleep hygiene
- Acupuncture/acupressure
- Massage
- Cupping
- Energy medicine
- Grounding
- Group Interaction
  - Decreased pain and depression, increased activity

Drinking Water

Key Supplements

- Vitamin D3
- Zinc
- Curcumin
- Vitamin C
- Quercetin
- B3
- Probiotic
- Vitamin A
- N-acetylcysteine (NAC)
- Melatonin
- Green tea (epigallocatechin gallate (EGCG)

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Exercise

Exercise

- Non-weight-bearing:
  - Swimming
  - Muscle-strengthening-quadriceps muscles
  - Recumbent bicycling
  - Walking
  - Cross-country skiing
  - Low impact aerobics
  - Pilates
  - Yoga
  - Reiki
  - Tai chi
  - Sauna for detox

Sleep

Personal Care Products

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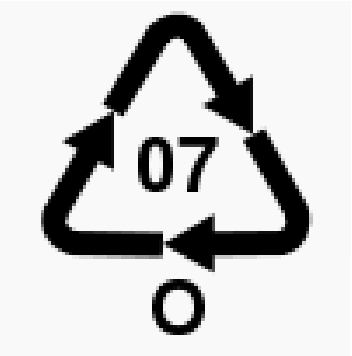
BPA: Avoiding Exposure

- Avoid microwaving plastic
- Buy less canned food
- Do not heat or dry plastics in dishwasher (DO not place plastic items on bottom shelf)
- If you don't need a receipt, tell you cashier you don't need one
- Avoid plastics marked with "7"



PLASTIC RESIN CODES

PETE	HDPE	V	LDPE	PP	PS	OTHER
Polyethylene Terephthalate	**High Density Polyethylene**	**Vinyl**	**Low Density Polyethylene**	**Polypropylene**	**Polystyrene**	**Other**
soda bottles	milk, water and juice jugs	clear food packaging	bread bags	ketchup bottles	meat trays	ketchup
water bottles	detergent bottles	shampoo bottles	frozen food bags	yogurt and margarine tubs	egg cartons	3 & 5 gallon water bottles
shampoo bottles	yogurt and margarine tubs		squeezable bottles (mustard, honey)		cups and plates	some juice bottles
mouthwash bottles	grocery bags					
peanut butter jars						

Guidelines for Environmentally Induced AID

- Strength of symptoms
- Consistency of symptoms
- Specificity of symptoms
- Cofounders
- Temporal relationship

YOU ARE THE DETECTIVE!

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Environmental History

- Where do you get your water from?
- How old is the house you live in?
- What types of personal care products do you use?
- What type of cleaning products do you use?
- Do you dust and vacuum your home regularly?
- What kind of floor covering do you have?
- Has your home been checked for radon?
- What is your occupation?
- Do you use insecticides in your home?
- Do you use flea and tick collars for your pets?
- Do you use canned, frozen or fresh foods?
- Do you have a fire alarm? A carbon monoxide detector
- Do you use candles, carpet cleaners and/or air fresheners?
- Do you handle any chemicals regularly?
- Are you on any medications?

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The NEW ENGLAND JOURNAL of MEDICINE

REVIEW ARTICLE

Caren G. Solomon, M.D., M.P.H., *Editor*

The Imperative for Climate Action to Protect Health

Andy Haines, M.D., and Kristie Ebi, M.P.H., Ph.D.

CLIMATE CHANGE IS ALREADY ADVERSELY AFFECTING HUMAN HEALTH and health systems,[1,2] and projected climate change is expected to alter the geographic range and burden of a variety of climate-sensitive health outcomes and to affect the functioning of public health and health care systems. If no additional actions are taken, then over the coming decades, substantial increases in morbidity and mortality are expected in association with a range of health outcomes, including heat-related illnesses, illnesses caused by poor air quality, undernutrition from reduced food quality and security, and selected vectorborne diseases in some locations; at the same time, worker productivity is expected to decrease, particularly at low latitudes.[3,4] Vulnerable populations and regions will be differentially affected, with expected increases in poverty and inequities as a consequence of climate change. Investments in and policies to promote proactive and effective adaptation and reductions in greenhouse-gas emissions (mitigation) would decrease the magnitude and pattern of health risks, particularly in the medium-to-long term.

Pearls

- The money is in the story!!!
- Childhood history! In utero hx??? We now know this hx matters!
- Don't inherit a previous diagnosis!!! Start from scratch
- If diet changes, change the meds! (allopurinol left on for years!!) Tx is fluid, not stagnant.
- Only change one thing at a time…the human body is an experiment!
- Get the patient "nutrient sufficient" first (assuming no acute issues) and see which symptoms fall away!
- Stress, sleep, drinking water, and environment matters!
- The human body yearns to heal itself!

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Resources

- Environmental Working Group www.ewg.org
- The National Environmental Education Foundation www.neefusa.org/
- EWG's Skin Deep Database www.ewg.org/skindeep
- The Endocrine Disruption Exchange www.endocrinedisruption.com
- Green Science Policy Institute http://greensciencepolicy.org/
- Environmental Defence http://environmentaldefence.ca/
- Natural Resources Defense Council www.nrdc.org
- Environmental Protection Agency www.epa.gov
- Centers for Disease Control and Prevention www.cdc.gov
- Consumer Reports Greener Choices www.greenerchoices.org
- Pediatric Environmental Health Speciality Units-PEHSU http://aoec.org/pehsu/facts.html#fact_sheets
- Health Care Without Harm www.noharm.org/us_canada/issues/toxins/pvc_phthalates/studies.php

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INTEGRATIVE

ENVIRONMENTAL MEDICINE

ALY COHEN, MD AND

FREDERICK S. VOM SAAL, PhD

WEIL INTEGRATIVE MEDICINE LIBRARY

DR. WEIL'S HEALTHY LIVING GUIDES

Non-Toxic

Guide to Living Healthy in a Chemical World

Aly Cohen, MD

Frederick S. vom Saal, PhD

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TEDx Talk:

How to Protect Your Kids from Toxic Chemicals

(YouTube)

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