Casual Friday Series

BPA and the Chemical Merry-Go-Round

A Biogenetix Clinical Presentation

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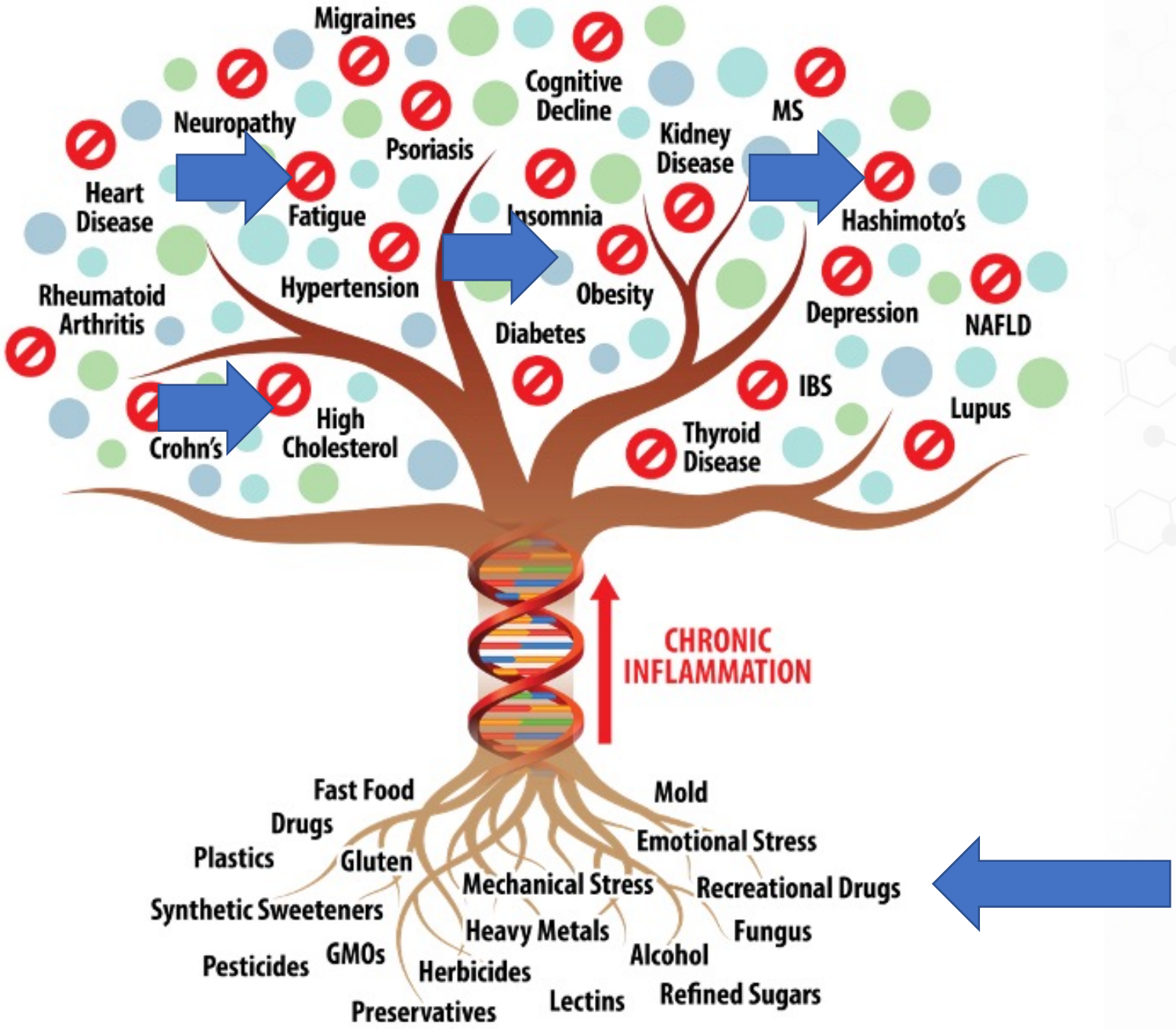
Migraines
Neuropathy
Psoriasis
Cognitive Decline
MS
Kidney Disease
Heart Disease
Fatigue
Insomnia
Hashimoto's
Hypertension
Obesity
Depression
NAFLD
Rheumatoid Arthritis
Diabetes
IBS
Lupus
Crohn's
High Cholesterol
Thyroid Disease
CHRONIC INFLAMMATION
Fast Food
Mold
Drugs
Emotional Stress
Plastics
Gluten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

BRIEF CORRESPONDENCE | VOLUME 7, ISSUE 4, P886-889, JULY 2021 Download Full Issue

Decline in Serum Testosterone Levels Among Adolescent and Young Adult Men in the USA

Soum D. Lokeshwar † • Premal Patel † • Richard J. Fantus • ... Cecilia Chang • Atil Y. Kargi • Ranjith Ramasamy • Show all authors • Show footnotes

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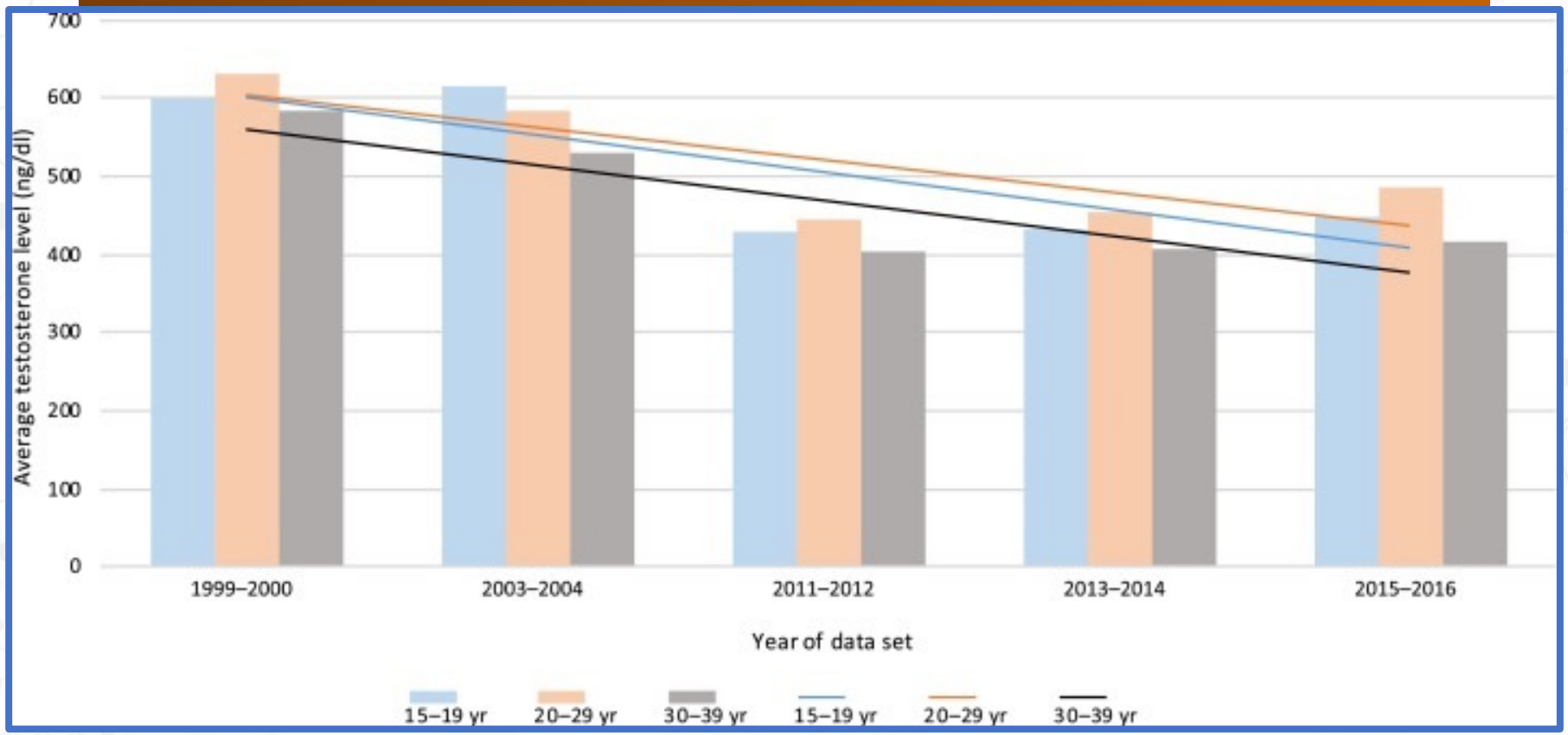
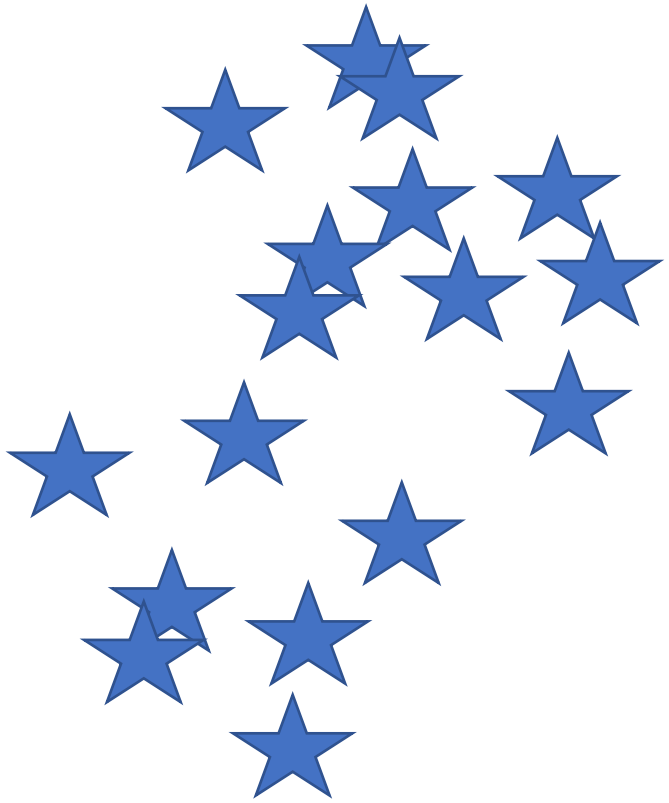
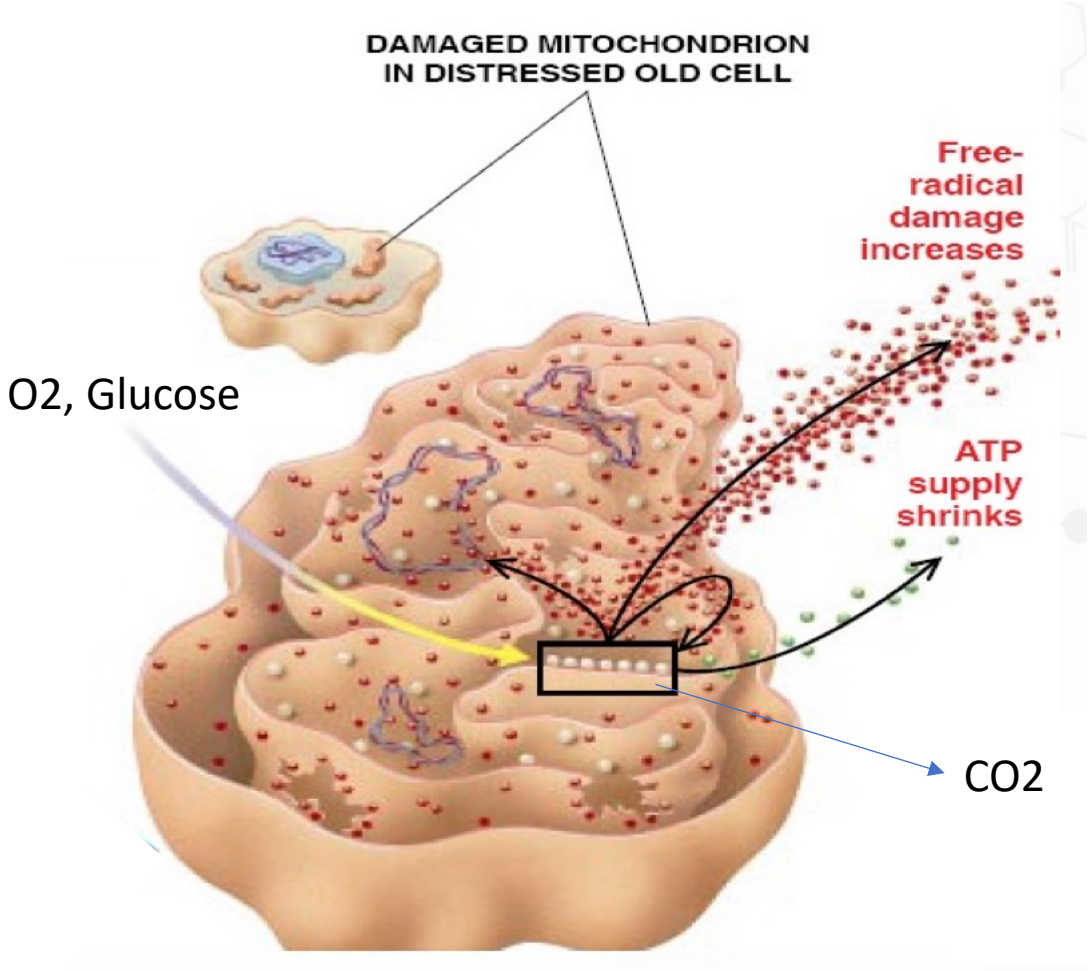





DAMAGED MITOCHONDRION
IN DISTRESSED OLD CELL
Free-
radical
damage
increases
ATP
supply
shrinks
O2, Glucose
CO2

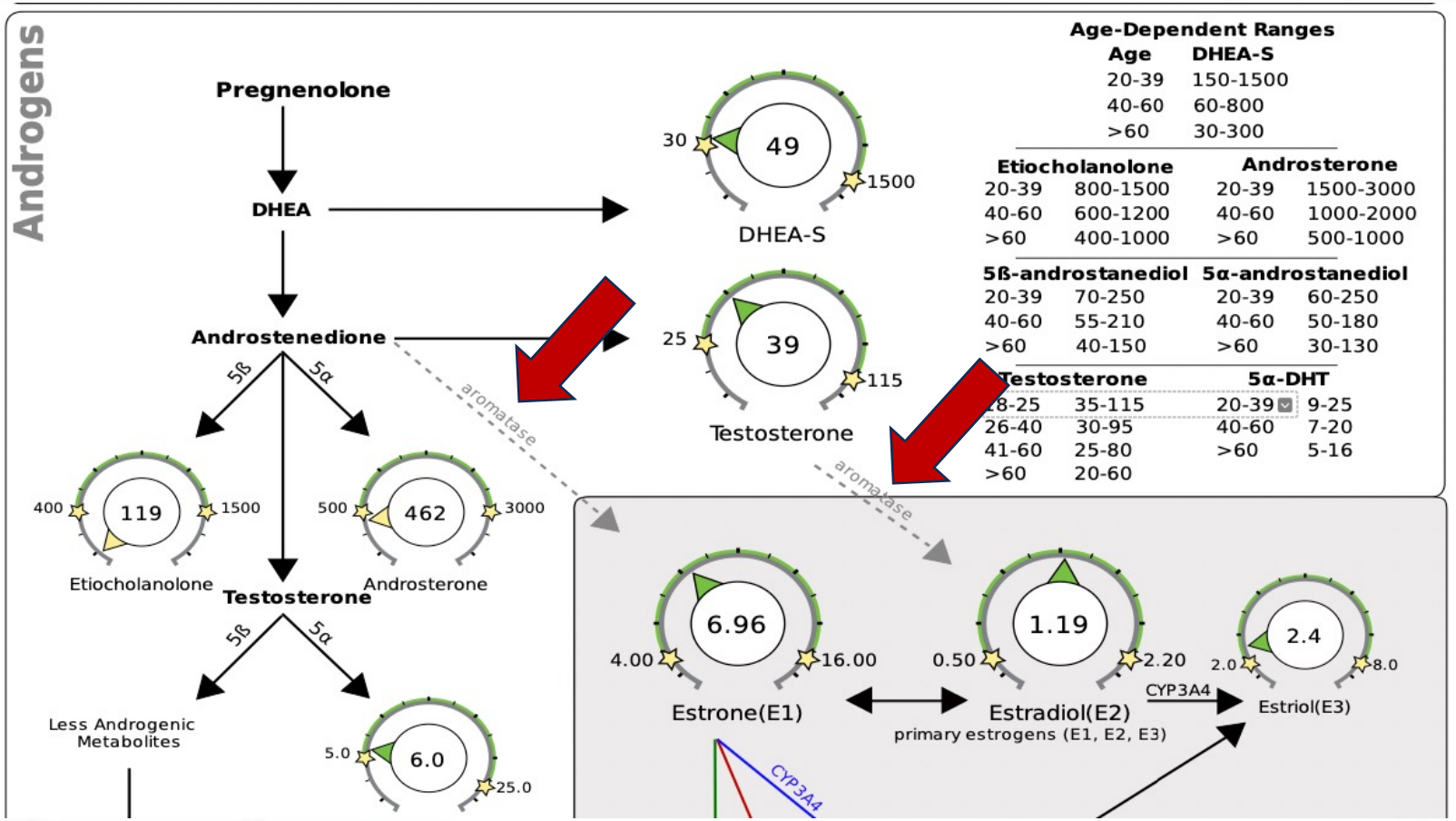
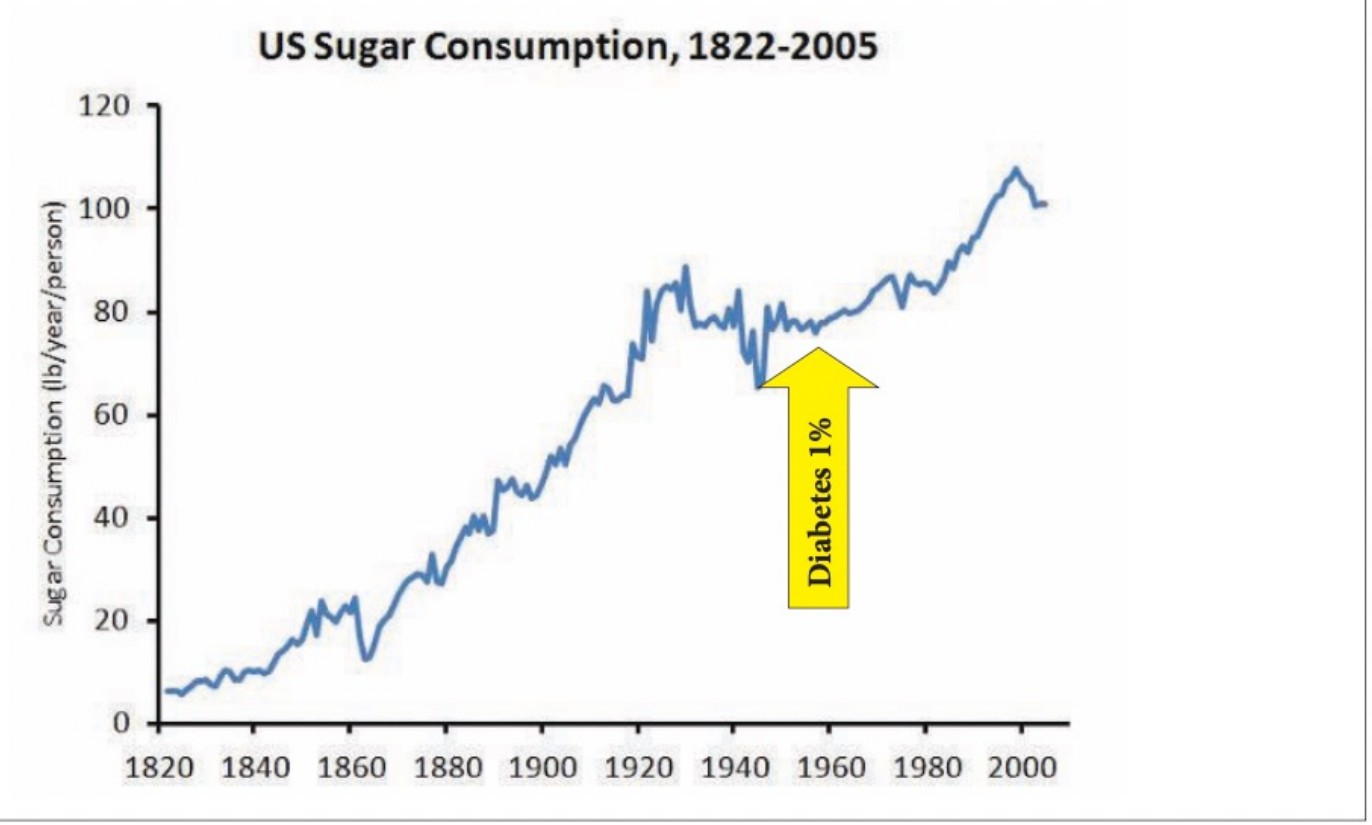
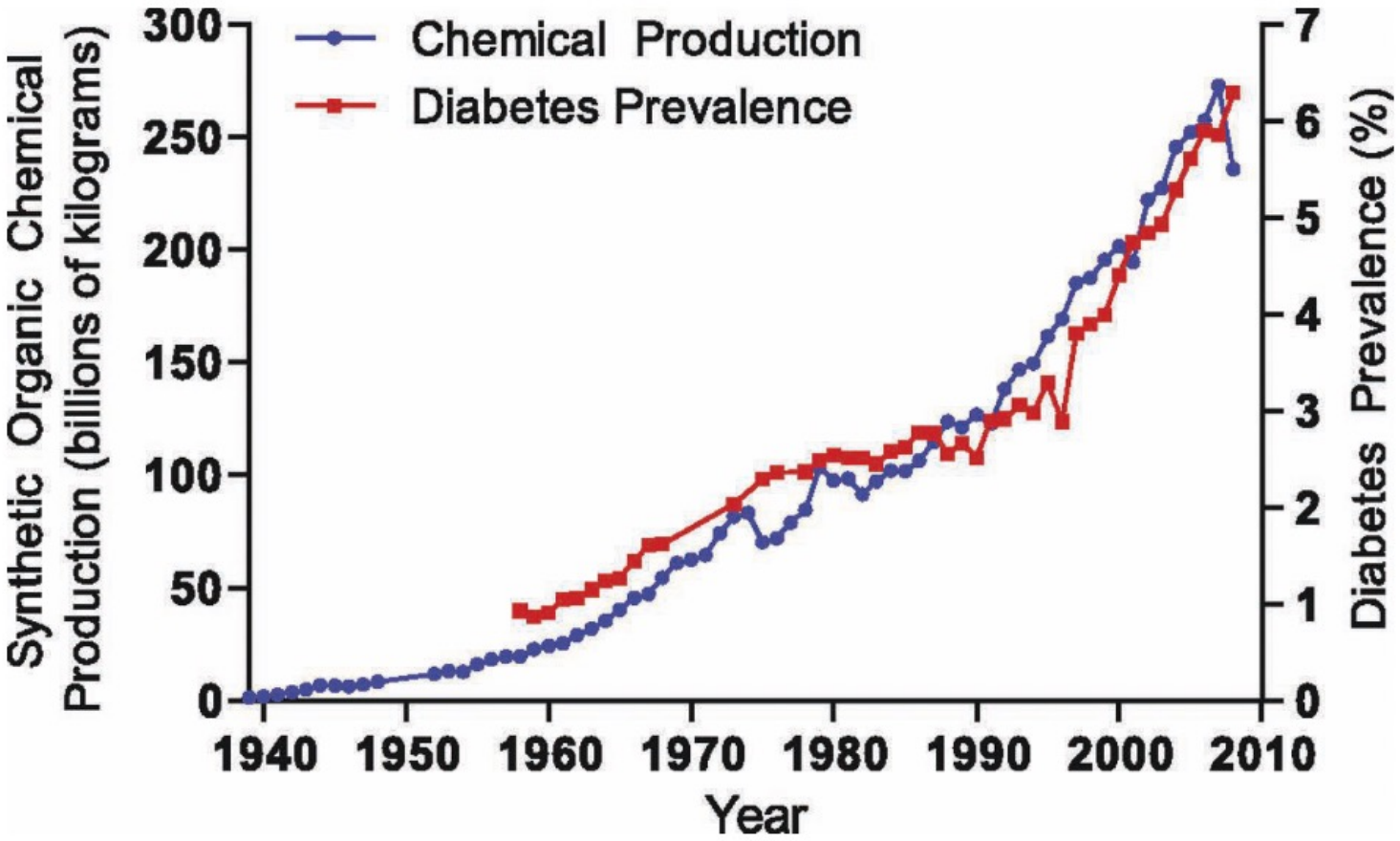

Androgens
Pregnenolone
DHEA
Androstenedione
Testosterone
Less Androgenic Metabolites
5ß
5α
aromatase
30
49
1500
DHEA-S
25
39
115
Testosterone
400
119
1500
Etiocholanolone
500
462
3000
Androsterone
5.0
6.0
25.0
4.00
6.96
16.00
Estrone(E1)
0.50
1.19
2.20
Estradiol(E2)
primary estrogens (E1, E2, E3)
CYP3A4
2.0
2.4
8.0
Estriol(E3)
Age-Dependent Ranges
Age DHEA-S
20-39 150-1500
40-60 60-800
>60 30-300
Etiocholanolone
20-39 800-1500
40-60 600-1200
>60 400-1000
Androsterone
20-39 1500-3000
40-60 1000-2000
>60 500-1000
5ß-androstanediol
20-39 70-250
40-60 55-210
>60 40-150
5α-androstanediol
20-39 60-250
40-60 50-180
>60 30-130
Testosterone
8-25 35-115
26-40 30-95
41-60 25-80
>60 20-60
5α-DHT
20-39 9-25
40-60 7-20
>60 5-16

Figure 2. The Diabetes Epidemic Does Not Correlate With the Increase in Sugar Consumption



https://pubmed.ncbi.nlm.nih.gov/27574488/

Figure 3. The Diabetes Epidemic Correlates With Release of POPs Into the Environment[4]



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Published online 2021 Jul 20. doi: 10.3389/fendo.2021.691658
PMCID: PMC8329539
PMID: 34354670

The Adipose Tissue at the Crosstalk Between EDCs and Cancer Development

Emma Bokobza, [1] Charlotte Hinault, [1,2] Victor Tiroille, [1] Stéphan Clavel, [1] Frédéric Bost, [1] and Nicolas Chevalier [1,2,*]

Obesity is a major public health concern at the origin of many pathologies, including cancers. Among them, the incidence of gastro-intestinal tract cancers is significantly increased, as well as the one of hormone-dependent cancers. The metabolic changes caused by overweight mainly with the development of adipose tissue (AT), insulin resistance and chronic inflammation induce hormonal and/or growth factor imbalances, which impact cell proliferation and differentiation. AT is now considered as the main internal source of endocrine disrupting chemicals (EDCs) representing a low level systemic chronic exposure. Some EDCs are non-metabolizable and can accumulate in AT for a long time. We are chronically exposed to low doses of EDCs able to interfere with the endocrine metabolism of the body. Importantly, several EDCs have been involved in the genesis of obesity affecting profoundly the physiology of AT. In parallel, EDCs have been implicated in the development of cancers, in particular hormone-dependent cancers (prostate, testis, breast, endometrium, thyroid). While it is now well established that AT secretes adipocytokines that promote tumor progression, it is less clear whether they can initiate cancer. Therefore, it is important to better understand the effects of EDCs, and to investigate the buffering effect of AT in the context of progression but also initiation of cancer cells using adequate models recommended to uncover and validate these mechanisms for humans. We will review and argument here the potential role of AT as a crosstalk between EDCs and hormone-dependent cancer development, and how to assess it.

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The development of some cancers is stimulated by hormones, which naturally circulate in the body and bind to membrane and/or nuclear receptors of cancer cells favoring their growth and multiplication. Among these hormone-dependent cancers, prostate cancer (PCa) and endometrial cancer (ECa) are the most common cancers of the male and female reproductive systems, respectively, in addition to breast cancer (BCa) which is the most common cancer in women worldwide (2). Steroid hormones (estrogens, androgens) play an important role in the etiology, progression and treatment of hormone-dependent cancers (11–13). It is therefore obvious that exposure to EDCs can influence the incidence and development of those cancers (9).

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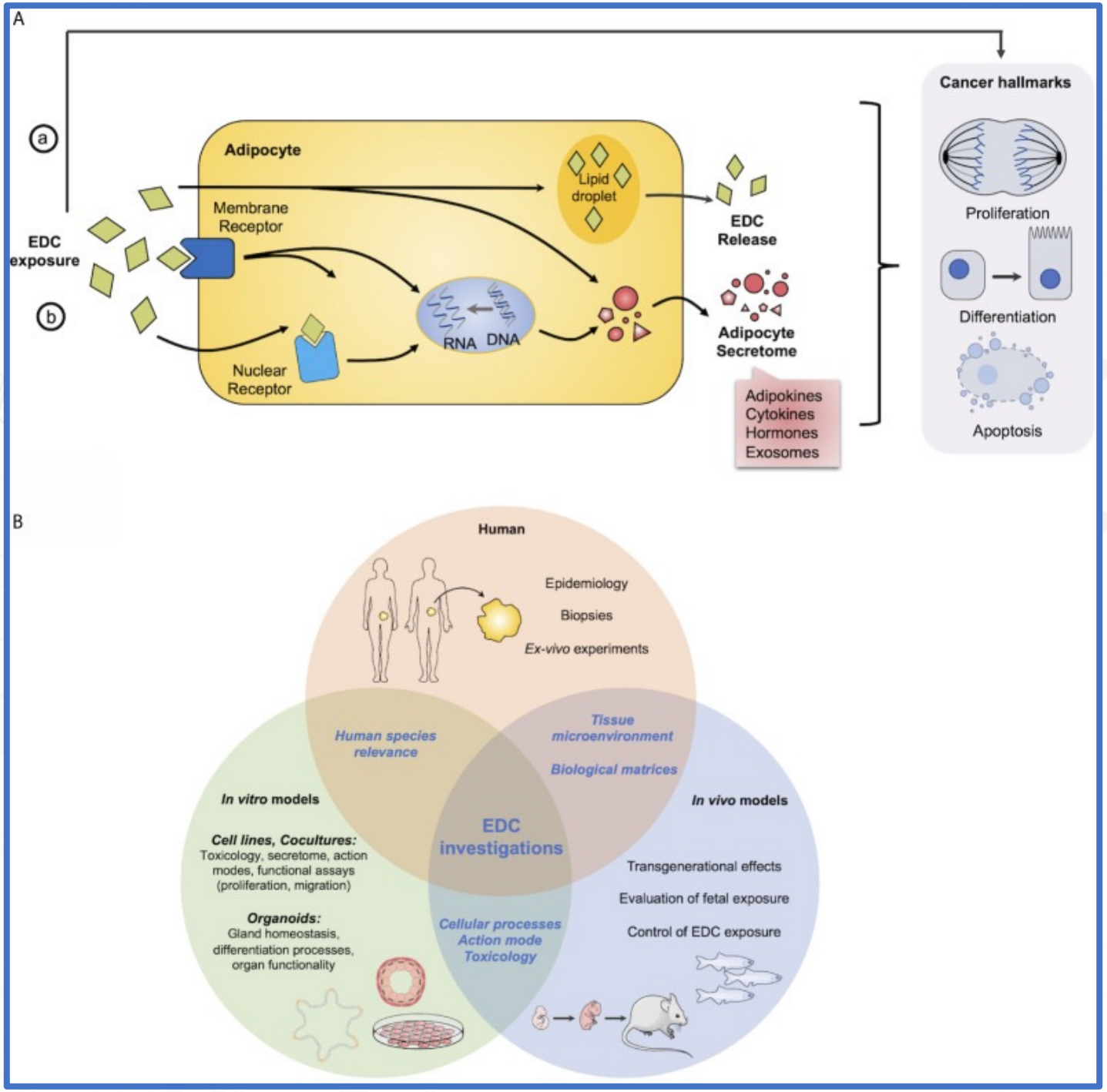
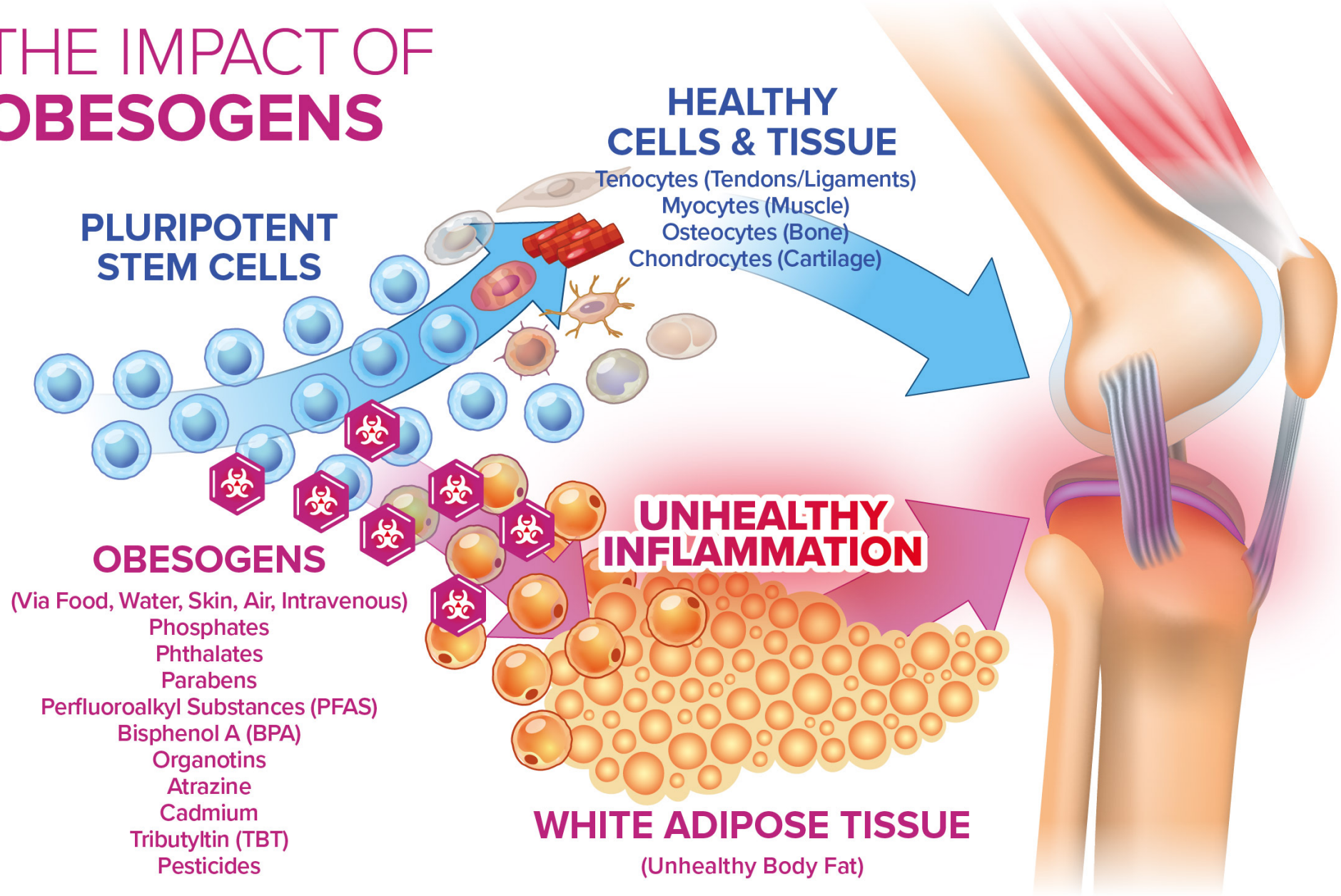
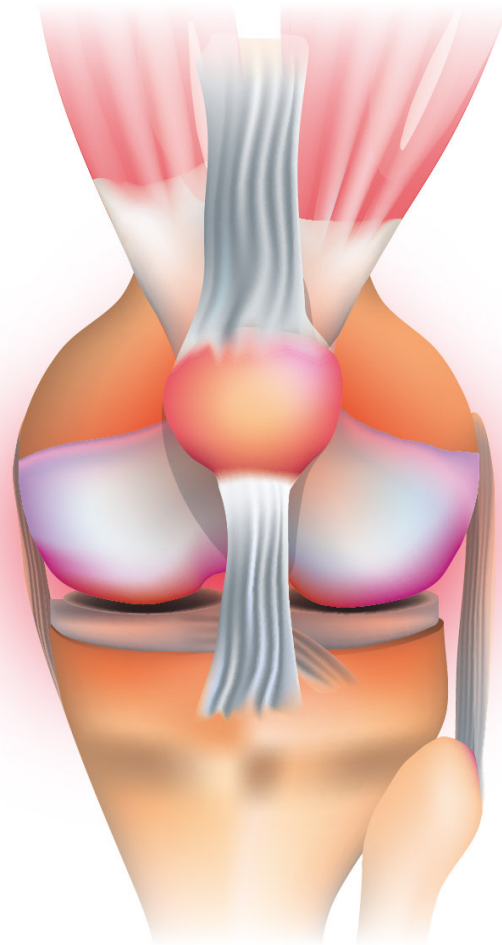
EDCs have been firstly identified as risk factor with the dramatic story of diethylstilbestrol (DES) (14). This synthetic diphenol with potent estrogenic properties was widely prescribed to pregnant women until 1970s to reduce the risk of abortion; however, several studies have reported an increased risk of rare cancers in women progenies (14, 15). Importantly, deleterious effects of prenatal DES exposure have been shown to persist in second-generation paving the way of the concepts of epigenetic transgenerational inheritance (16). Since then, several epidemiological studies supported by *in vivo* and *in vitro* experiments have confirmed this association between EDCs (notably PCBs, dioxins, DDE and bisphenol A [BPA]) and an increased risk of hormone-dependent cancers in both sexes (7, 17–19). Regarding testicular cancer, we and others have shown that BPA was able to stimulate the proliferation of seminoma cells involving GPR30/GPER pathway (20–22). Concerning PCa, Prins et al. have shown that exposure to BPA makes prostate stem cells more sensitive to estrogen in adulthood and therefore more likely to develop PCa (23, 24). Regarding persistent EDCs, although discussed, exposure to chlordecone constitutes a demonstrative example with a significant increase in the risk of PCa (25) and of recurrence after radical prostatectomy (26). Observational and experimental studies have suggested a role of PCB-153, an industrial organochlorine product, in the development of high-grade PCa (27). However, a previous study observed an inverse correlation between plasma concentrations of PCB-153 and PCa (28). Likewise, studies differ about a positive association (29) or not (30) between elevated serum levels of PFOA and PCa onset and/or progression. Thus, despite this extensive work on the role of certain EDCs in the incidence of hormone-sensitive cancers, diverse investigations for their action modes, their effects on tumor growth and on the formation of metastases especially in human are still poorly understood (7, 31).


A
a
b
EDC exposure
Adipocyte
Membrane Receptor
Nuclear Receptor
Lipid droplet
RNA
DNA
EDC Release
Adipocyte Secretome
Adipokines
Cytokines
Hormones
Exosomes
Cancer hallmarks
Proliferation
Differentiation
Apoptosis
B
Human
Epidemiology
Biopsies
Ex-vivo experiments
Human species relevance
Tissue microenvironment
Biological matrices
In vitro models
Cell lines, Cocultures:
Toxicology, secretome, action modes, functional assays (proliferation, migration)
Organoids:
Gland homeostasis, differentiation processes, organ functionality
EDC investigations
Cellular processes
Action mode
Toxicology
In vivo models
Transgenerational effects
Evaluation of fetal exposure
Control of EDC exposure

THE IMPACT OF **OBESOGENS**



THE **ADIPOKINE** SPIRAL



1 Obesogens Drive Stem Cells into Adipocytes

2 Adiposity Increases

3 Increased Adipokine Activity

4 Triggering Increased Unhealthy Inflammation

5 Ongoing Tissue Damage

Endocrine disrupting effects of bisphenol A exposure and recent advances on its removal by water treatment systems. A review

Okugbe

Bisphenols (BPA) are phenolic, organic synthetic compounds used as an additive or monomers in the production of polycarbonate plastics and epoxy resins. BPA is a reproductive, developmental, and systemic toxicant, often classified as an endocrine-disrupting compound (EDC). BPA absorption into the body can result in the development of metabolic disorders such as low sex-specific neurodevelopment, immune toxicity, neurotoxicity and interference of cellular pathway. Therefore, the presence of BPA and its analogues in the environment has recently attracted global attention. This review provides evidence of BPA as a harmful compound and summarizes the current state of science on its removal. Several BPA removal techniques that mainly comprised of biological treatment, advanced oxidation and adsorption process were extensively studied. Biological treatment methods involved the use of biological agents such as enzymes (notably, laccase and peroxidase enzyme) to induce a degradation effect on bisphenols, and converting them into relatively harmless and less toxic compounds. Although, the removal efficiencies varied, the efficiencies for BPA by biological techniques was about 84%. Advance oxidation (AO) technique involves the use of highly reactive radical to degrade BPA. Hydroxyl (HO) and sulfate radical (SO_4^-) were the most commonly used radicals for BPA degradation. BPA removal by application of adsorption process were also discussed.

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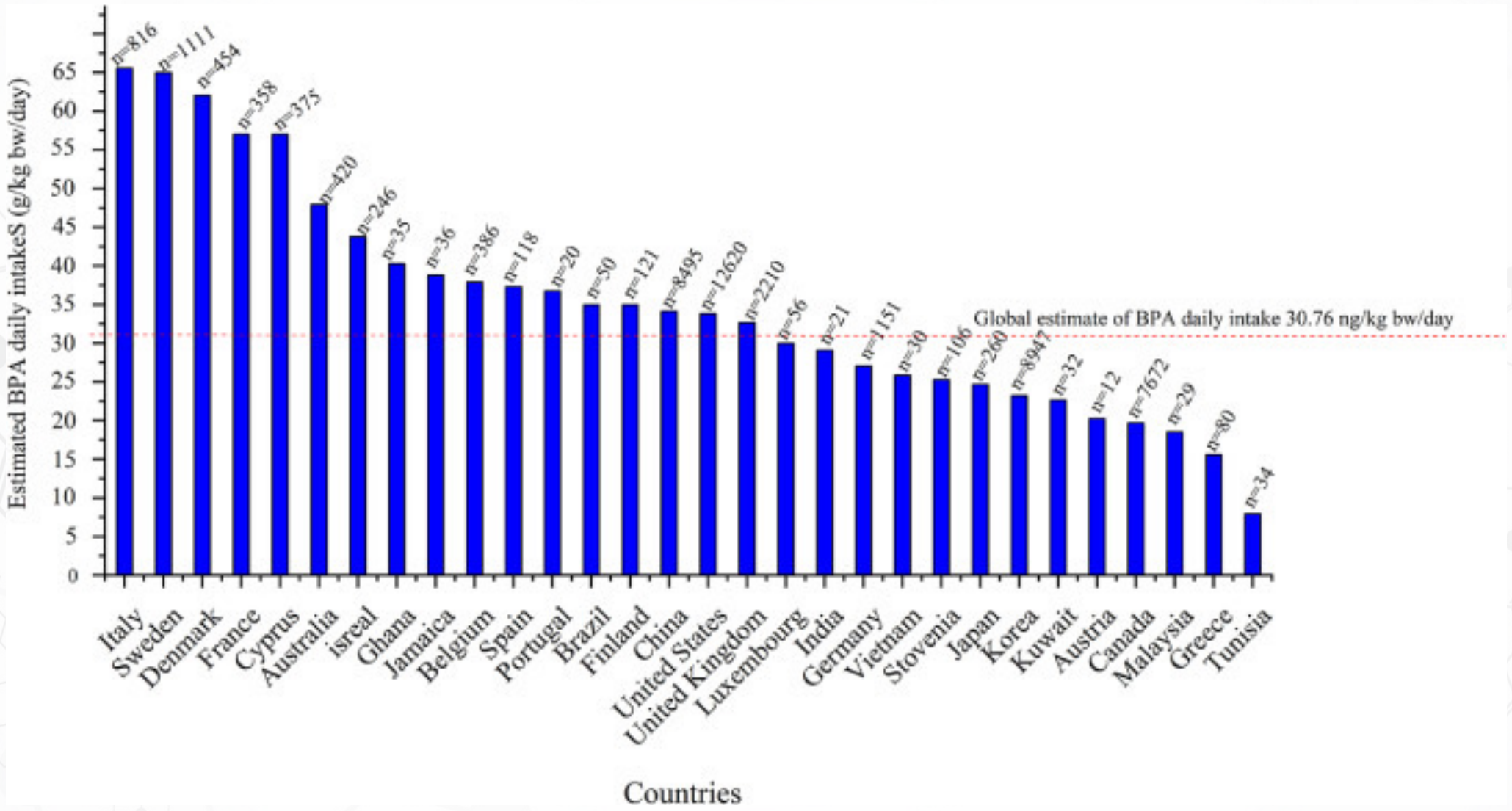

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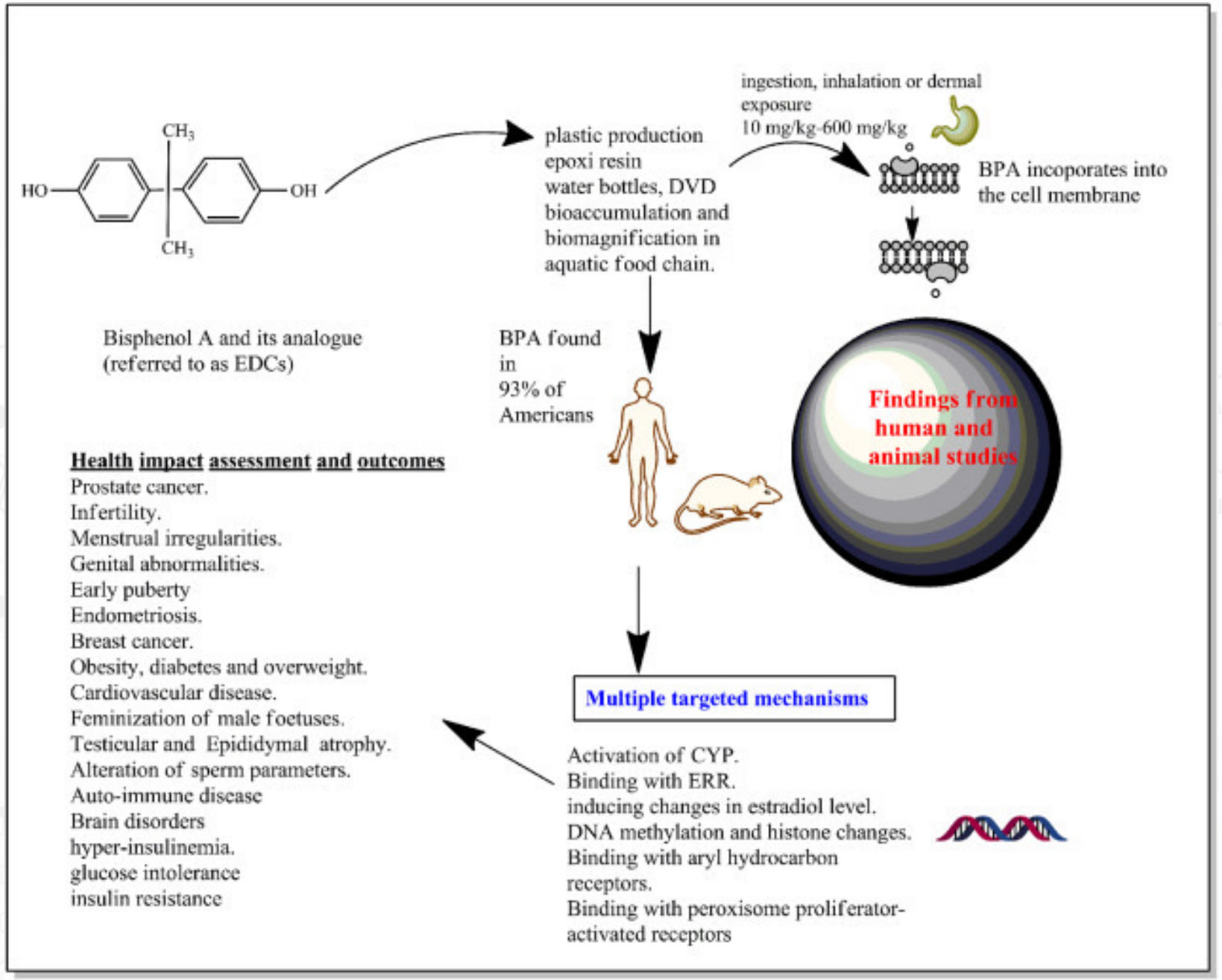

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Endocrine disrupting effects of bisphenol A exposure and recent advances on its

In males, exposure to high serum concentration of BPA (1.53–2.22 μg/L) especially during developmental stage resulted in feminization of male foetuses, testicular and epididymal atrophy, alteration of sperm parameters, and reduction of testosterone levels [22]. Possible mechanism is that BPA induces c-Jun phosphorylation which contributed to activation of cytochrome P450 genes (CYP gene) expression in both mRNA and protein levels, which resulted in alteration of the normal sex hormone ratio [23]. Many studies have shown that the overall effects of BPA on the male reproductive system have shown to be more pronounced in the fetal period [24].

In females, high serum concentration of BPA (1.53–2.22 μg/L) induces changes in estradiol E_2, which resulted to distortion of hormonal balance and metabolic abnormalities such as early puberty, menstrual irregularities, increased likelihood of endometriosis, higher implantation failure, and ineffective gonadotropin fertility treatment [25]. Numerous reports have suggested that BPA binds with estrogen related-receptors (ERα and ERβ), aryl hydrocarbon receptors and peroxisome proliferator-activated receptors, and induction of alternative estrogen signaling. Lastly, the effects of BPA paradigm of estrogen possesses stronger signaling than equimolar concentration estrogen [26].

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Endocrine disrupting effects of bisphenol A exposure and recent advances on its removal by water treatment systems. A

Effects on regulation of glucose level

Effects of BPA exposure on glucose regulation have been extensively studied. Reports indicated that exposure to high level of BPA (10–400 mg/kg) caused oxidative stress and disruption of pancreatic β-cell function [36] and resulted in complication in glucose regulation [37], [38], [39]. BPA caused islet differentiation and a delay in the conversion of islet cell clusters (ICCs) into matured islets (ICCs level was <300 μm), resulting in excessive glucagon expression [37] and alteration of αβ cells ratios in islet [40]. BPA exposure was tested on mice to know its effect on insulin signaling in brain, it was discovered that, in fetal mice (8months of age) offspring, the insulin signaling including insulin phosphorylated extracellular signal regulated protein kinase (p-ERK) and glucose transporter (GLUT) were significantly decreased. Also, hyper-insulinemia, glucose intolerance and insulin resistance were reported to be associated with BPA exposures [41]. This showed that bisphenol analogues have a negative impact on glucose metabolism (Table S3). BPA is conjugated primarily to mono-glucuronide in rat liver, deconjugated condition occurred in high dose exposure to BPA and the resultant metabolites were excreted into the bile [42].

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Endocrine disrupting effects of bisphenol A exposure and recent advances on its removal by water treatment systems. A review

Effects of BPA on the cardiovascular system

Exposure to BPA and its effects on the cardiovascular system were studied. Reports suggested a possible relationship between BPA exposure and hypertension [43], [44], [45], [46] and it severely affects the cardiovascular system during a hypoxic event [47]. BPA affects angiogenesis by stimulating the production of vascular endothelial growth factor, causing uncontrolled neovascularization [48] and increase in interventricular septal thickness [49]. It was also reported that exposure to BPA with varying concentration of 1–250 μg/mL, caused an increase in calcium levels in incubated erythrocyte with the strongest effect noted for BPAF, and BPF (bisphenol analogues) which particularly resulted in increased phosphatidylserine translocation in red blood cells [50] and arrhythmias [51]. This confirms its deleterious effect on the cardiovascular system.

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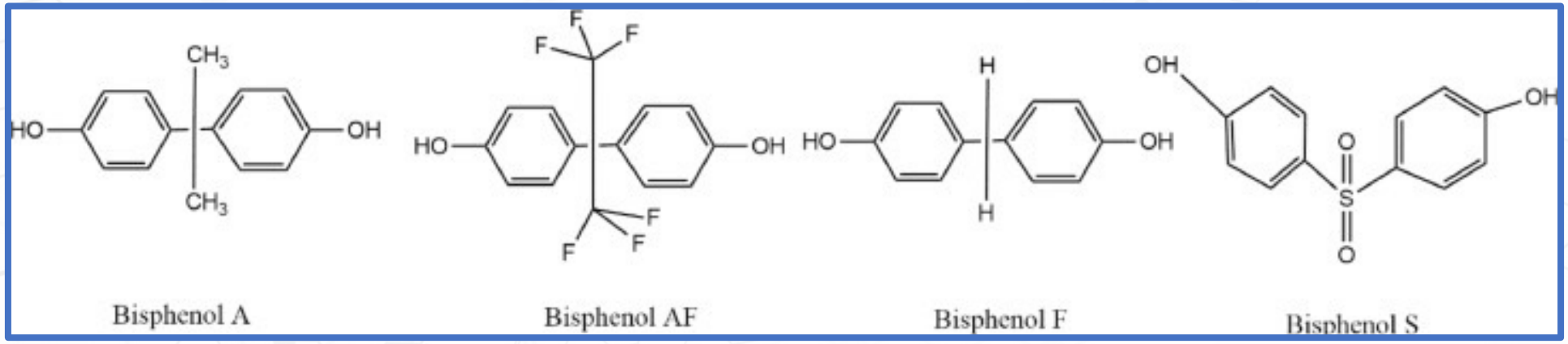

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Hormone Testing Summary

Key (how to read the results):

Sex Hormones

Estradiol(E2)

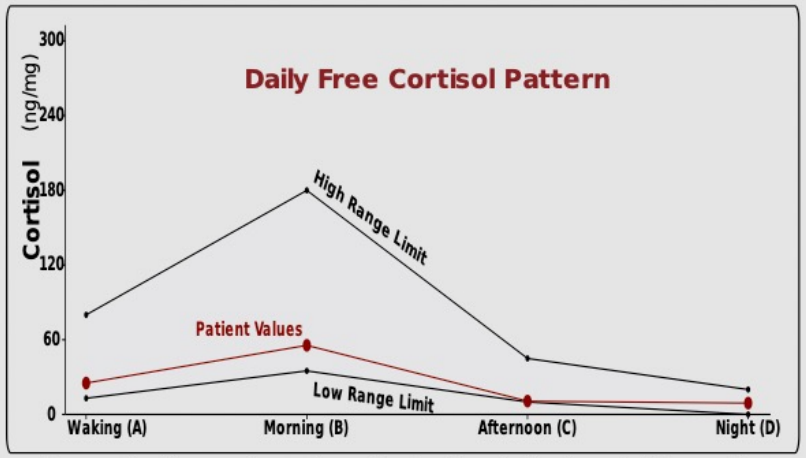
Testosterone

Testosterone

Age	Range
18-25	35-115
26-40	30-95
41-60	25-80
>60	20-60

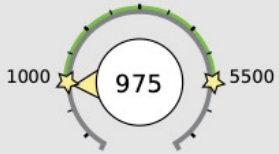
Adrenal Hormones

See pages 4 and 5 for a more complete breakdown of adrenal hormones



Total DHEA Production

Age	Range
20-39	3000-5500
40-60	2000-4000
>60	1000-2500



Total DHEA Production
(DHEAS + Etiocholanolone + Androsterone)

24hr Free Cortisol
(A+B+C+D)

cortisol metabolism →

Metabolized Cortisol (THF+THE)
(Total Cortisol Production)

Free cortisol best reflects tissue levels. Metabolized cortisol best reflects total cortisol production.

Moderate (75th-95th percentile)

Mycotoxins | Heavy Metals | Environmental Toxins

TEST NAME	CURRENT RESULT	PREVIOUS RESULT	CURRENT RESULT / PREVIOUS RESULT	REFERENCE
Mycophenolic Acid	5.15			≤6.4 ng/g
Antimony*	0.09			≤0.16 ug/g
Cesium*	7.38			≤10.3 ug/g
Nickel	9.69			≤12.13 ug/g
Bisphenol A (BPA)*	4.52			≤5.09 ug/g
Butylparaben*	0.46			≤4.39 ug/g
Glyphosate	3.75			≤7.6 ug/g

* Indicates NHANES population data reference ranges.

Hormone Testing Summary

Key (how to read the results):

Sex Hormones

Estradiol(E2)

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Testosterone

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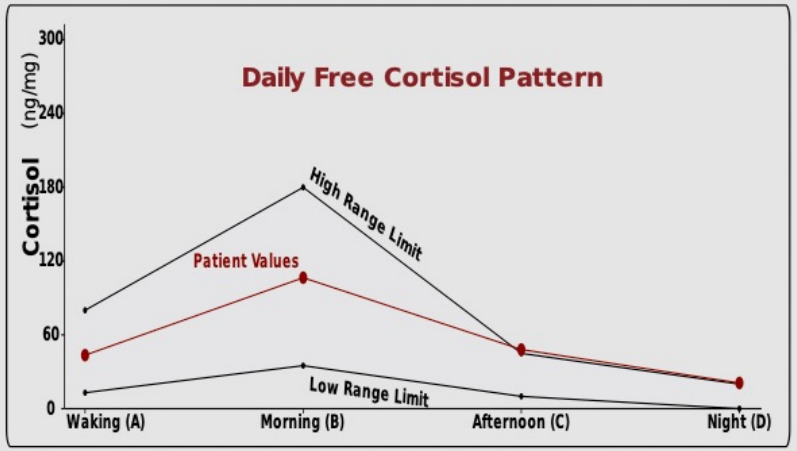

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Age	Range
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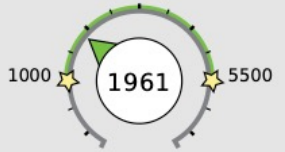


Total DHEA Production
(DHEAS + Etiocholanolone + Androsterone)

24hr Free Cortisol
(A+B+C+D)

cortisol metabolism

Metabolized Cortisol (THF+THE)
(Total Cortisol Production)

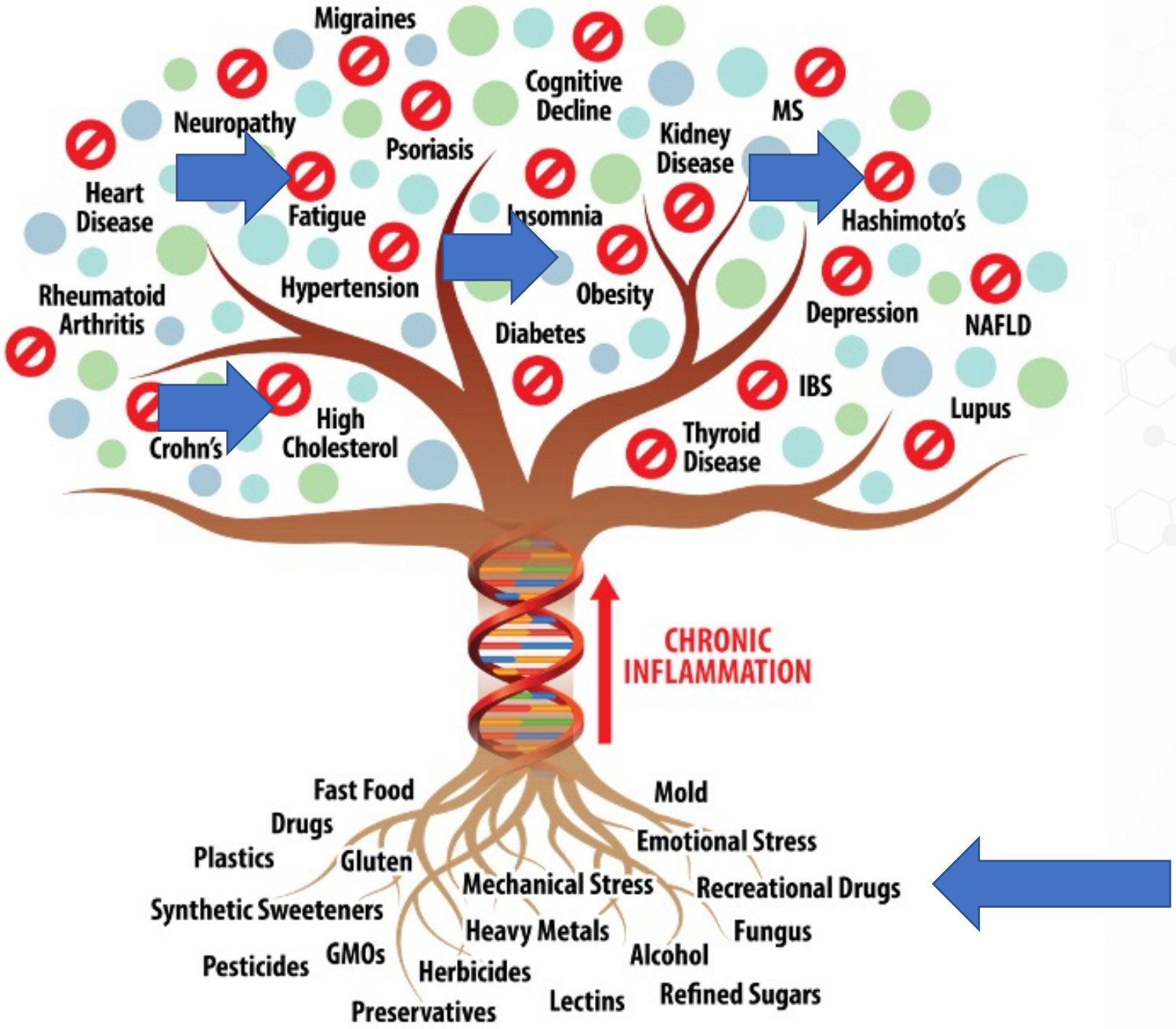
Free cortisol best reflects tissue levels. Metabolized cortisol best reflects total cortisol production.

High (>95th percentile)

Mycotoxins | Heavy Metals | Environmental Toxins

TEST NAME	CURRENT RESULT	PREVIOUS RESULT	CURRENT RESULT / PREVIOUS RESULT	REFERENCE
Aflatoxin G2	15.45		0 — 6.08 — 10.8	≤10.8 ng/g
Ochratoxin A (OTA)	11.18		0 — 3.83 — 6.8	≤6.8 ng/g
Thallium*	1.9		0 — 0.24 — 0.43	≤0.43 ug/g
Uranium*	1.27		0 — 0.02 — 0.04	≤0.04 ug/g
Bisphenol A (BPA)*	9.38		0 — 2.12 — 5.09	≤5.09 ug/g
Glyphosate	19.22		0 — 1.65 — 7.6	≤7.6 ug/g

* Indicates NHANES population data reference ranges.


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