

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/316518314>

The Chemical Disruption of Human Metabolism

Article in *Toxicology mechanisms and methods* · April 2017

DOI: 10.1080/15376516.2017.1323986

CITATIONS

0

READS

525

2 authors:



Stephen Genuis

University of Alberta

124 PUBLICATIONS 1,653 CITATIONS

[SEE PROFILE](#)



Edmond Kyrillos

University of Ottawa

2 PUBLICATIONS 6 CITATIONS

[SEE PROFILE](#)

Some of the authors of this publication are also working on these related projects:



Current Project: Preparation of an online video series entitled "An Environmental Medicine Approach to Patient Care" at [www.stephengenuis.com]. [View project](#)



Toxic elements in nutrition [View project](#)

All content following this page was uploaded by [Stephen Genuis](#) on 08 October 2017.

The user has requested enhancement of the downloaded file.



Journal

Toxicology Mechanisms and Methods

Review Article

The Chemical Disruption of Human Metabolism

Stephen J. Genuis & Edmond Kyrillos

Pages 1-62

Received 25 Feb 2017, Accepted 23 Apr 2017,

Accepted author version posted online: 26 Apr 2017

Official publication at <http://dx.doi.org/10.1080/15376516.2017.1323986>

The Chemical Disruption of Human Metabolism

by

Stephen J. Genuis & Edmond Kyrillos

Type of Paper: *Substantive Review*

Dr. Stephen J. Genuis is a Clinical Professor and Researcher at the University of Alberta. He is also affiliated with the University of Calgary.

Dr. Edmond Kyrillos is an independent researcher with a special interest in Environmental Health. He is affiliated with the University of Ottawa. ekyrillo@uottawa.ca

Correspondence to: Dr. Stephen J. Genuis (sgenuis@shaw.ca)

There are no conflicts of interest. No funding has been received for any part of this work.

The Chemical Disruption of Human Metabolism

Stephen J. Genuis & Edmond Kyrillos

Abstract

Background: Recent evidence highlights the reality of unprecedented human exposure to toxic chemical agents found throughout our environment - in our food and water supply, in the air we breathe, in the products we apply to our skin, in the medical and dental materials placed into our bodies, and even within the confines of the womb. With biomonitoring confirming the widespread bioaccumulation of myriad toxicants among population groups, expanding research continues to explore the pathobiological impact of these agents on human metabolism.

Methods: This review was prepared by assessing available medical and scientific literature from Medline as well as by reviewing several books, toxicology journals, government publications, and conference proceedings. The format of a traditional integrated review was chosen.

Results: Toxicant exposure and accrual has been linked to numerous biochemical and pathophysiological mechanisms of harm. Some toxicants effect metabolic disruption via multiple mechanisms.

Conclusions: As a primary causative determinant of chronic disease, toxicant exposures induce metabolic disruption in myriad ways, which consequently result in varied clinical manifestations, which are then categorized by health providers into innumerable diagnoses. Chemical disruption of human metabolism has become an etiological determinant of much illness throughout the lifecycle, from neurodevelopmental abnormalities in-utero to dementia in the elderly.

Key words: biochemistry, chemical agents, toxicants, epigenetics, endocrine disruption, sensitivity-related illness, detoxification pathways, metabolic pathways, metabolism, multimorbidity, mitochondria, oxidative stress, immune dysfunction.

Table of Contents

I. Introduction and Background	4
a. From Etiology to Clinical Symptoms	5
b. Methodology	7
II. Cytotoxic Mechanisms of Harm	8
a. Direct Damage to Cell Structures	9
b. Oxidative Stress	10
c. Receptor Dysregulation	12
d. Epigenetic Alteration	13
e. Cellular Detoxification Impairment	14
f. Plaque formation	16
g. Displacement	17
h. Other mechanisms of cellular toxicity	18
III. Pathophysiological Mechanisms of Harm	19
a.. Endocrine Disruption	19
b. Inflammation	21
c. Immune Dysfunction	22
d. Pathway Dysregulation	25
e. Biome Alteration	26
f. Autonomic Nervous System dysregulation	28
g. Neurotransmission Dysfunction	26
h. Nutritional Compromise	30
i. Other mechanisms of pathophysiological harm	30
IV. Limitations	31
V. Concluding Thoughts	33
VI. Tables & Figures	34
References	47

The Chemical Disruption of Human Metabolism

Environmental pollution is an incurable disease. It can only be prevented.

Barry Commoner

I. Introduction and Background

In a colossal toxicological experiment carried out over the last few decades, there has been the unprecedented production and release of tens of thousands of chemical agents into the environment without sufficient consideration for human safety and without credible testing to secure the absence of danger or harm. Such chemical pollutants are now ubiquitous and surreptitiously linger within our foods, our air, our water, and even within our bodies.[1, 2] (Figure 1) In the last few years, emerging research, as explored in this paper, has begun to elucidate the unfolding consequences of this dubious experiment.

Rather than rapidly exiting the human body, some chemical pollutants persist for extended periods[3, 4] primarily because of i) ongoing reabsorption in the enterohepatic circulation,[5] ii) limited detoxification capabilities of humans compared to other species,[6] and iii) selective affinity of some chemicals for specific sites of retention – such as brain adipose tissue for various lipophilic chemicals, or bone tissue for the toxic element lead. (Figure 2) The ongoing presence of bioactive chemical agents has a well-recognized impact on biological processes. While some feel the documented levels of such agents in the human body are insufficient to cause harm, ongoing research shows otherwise.[7]

Standard biochemicals within our inherent physiology, as well as prescribed pharmaceutical agents, are often bioactive at levels of parts per billion (ppb), and some at parts per trillion (ppt). (Table 1) For example, normal estradiol levels in reproductive-aged women regulate hormonal processes at serum levels as low as 30 pg/ml. It is hardly surprising, therefore, that serum concentrations of various bioactive chemical toxicants often reported in ppb or ppm (parts per million) might also have biological impact on the human organism. In fact, it has become apparent that myriad chemical agents exert significant impact at seemingly miniscule doses,[7, 8] with

incremental influence for many pollutants at increasing levels of accrual.[9, 10] But what do these chemicals actually do to human biology and biochemistry?

As a community of cells, the human organism has many sites and myriad metabolic processes confirmed to be targets of specific chemical agents. Emerging science has uncovered various mechanisms by which chemical pollutants disrupt normal biochemical and physiological functioning. This paper will explore the scientific literature to provide an overview of the assorted ways that chemical toxicants perturb and distort the metabolism and homeostasis of the human body.

1a..... From Etiology to Clinical Symptoms

The study of human biochemistry and physiology explores the normal requisite metabolic pathways and processes that are fundamental to the functioning of the human organism. The field of pathophysiology, on the other hand, explores disordered or disrupted homeostasis and metabolic function in order to understand and potentially treat altered mechanisms that are characteristic of specific diseases. The etiology or root cause of illness refers to determinants which elicit the change from normal biochemistry and physiology to disordered biochemistry and physiology. Clinical signs and symptoms are the manifest expression of such disordered biology. (Figure 3) Medications used to treat disease, other than antimicrobials, generally involve the use of molecules designed to overcome the pathobiological changes in metabolism in order to relieve manifest signs and symptoms resulting from disordered processes. The underlying etiology or root cause of such pathobiological processes, however, is frequently not explored in contemporary medical practice.[11]

Throughout history, conversely, much focus has been devoted to the study of disease etiology or “what’s out there making us sick?”[12] While various beliefs about disease causation have been dogmatically promoted at various times throughout the ages, much of the focus of contemporary healthcare has presumed a primarily genomic basis for chronic disease. Energies in clinical practice are thus usually directed at categorizing signs, symptoms, and laboratory data into diagnoses and then treating illness by instructing patients to ‘take this for that,’ as dictated by the

most recent clinical practice guidelines. While thick textbooks and abundant medical literature expound on the countless diagnoses and associated treatments studied by medical trainees and applied by health professionals in clinical situations, the provision of suggested medications and interventions to mitigate symptoms has been unable to stem the oft neglected and rising tide of chronic illness that plagues our culture.[13, 14]

Recent scientific evidence suggests that rather than being the result of celestial genetic roulette, metaphysical destiny, or simply bad luck, illness appears to commence because of a cause (or causes), persists because the cause persists, and fully resolves only when the cause is found and addressed.[15] Both medical history and emerging science confirm that only a handful of primary determinants are the underlying etiological factors leading to the myriad diagnoses or labels we use to categorize patterns of signs and symptoms into diagnoses.[12] In other words, it appears that science consistently demonstrates that there are many ways of being sick, but only a few ways of becoming sick.[12, 16] The Centre for Disease Control recently confirmed that virtually all illness is the result of genomic predisposition in combination with environmental factors[17] and a recent article in the journal *Science*, goes on to suggest that 70-90% of all disease is primarily the result of modifiable environmental factors.[18] Other publications in the literature also confirm the enormous contribution of environmental determinants to the etiology of specific chronic diseases.[19, 20] A predominant environmental factor long ago identified and confirmed to be a consistent determinant of illness is exposure to toxic chemical agents.[21]

While acute poisoning has long been recognized and studied as a cause of acute illness, Paracelsus sometimes known as the Father of Toxicology, recognized in the sixteenth century that ongoing low dose toxic exposures may also be an etiological determinant of illness prompting him to write about diseases of miners and the occupational hazards of metalwork.[21] More recently, it has been confirmed that chronic low dose exposure to many kinds of toxic chemical agents is a potential causative determinant of human illness.[7, 22] In this paper, we will discuss much of what the recent scientific literature has elucidated with regards to toxic chemical exposures and the mechanisms by which these agents induce metabolic disruption and ultimately clinical illness.

Ib.....Methodology

This review of mechanisms of toxic chemical harm was prepared by assessing available medical and scientific literature from Medline as well as by reviewing several books, toxicology journals, government publications, and conference proceedings. Terms searched included toxicants and pathology, toxicants and metabolism, toxicants and biochemistry, toxicants and pathophysiology, toxicants and biology, as well as toxicants and physiology. Relevant references found in these publications were also searched in order to glean pertinent information.

General classifications for metabolic mechanisms of harm were then identified and used as headings in this paper. (Table 2) Searching was subsequently undertaken according to each of the mechanisms listed. As the subject matter for this review is quite broad, a brief synopsis of available information in each section was prepared with the intention of providing an overview of the issue of toxicants and metabolism for clinical practitioners involved in environmental health sciences, occupational health, primary care, and all other relevant disciplines of healthcare provision. More detailed information on each of the mechanisms can be found in the papers referenced.

A traditional integrated review format was chosen for this paper.[23] This type of publication approach seemed apposite when endeavoring to incorporate and synthesize extensive literature in a new and emerging field with limited primary study, while at the same time endeavoring to provide a clinically useful overview of highly detailed and scientific information to clinical and public health professionals.

In this paper, classification for biochemical and pathophysiological mechanisms of harm was divided into two categories: toxicity primarily occurring directly at the cellular level, followed by potential mechanisms of physiological alteration. (Table 2) The classification is arbitrary with considerable overlap in the mechanisms of harm discussed, as biochemical cellular change typically results in some type(s) of pathophysiological alteration. Furthermore, some metabolic outcomes result from several kinds of toxic mechanisms – such as disruption of thyroid hormone

homeostasis occurring from receptor dysregulation, autoantibody production, or pathway inhibition of deodinase enzymes.[24, 25] (Table 3)

In addition, chain reactions of metabolic disruption might occur as one toxic action may prompt another and then another, resulting in a cascade of altered outcomes. For example, toxic chemical agents may induce oxidative stress which may result in mitochondrial damage, which may prevent normal cell demise, which may produce inflammatory changes in tissues, which may cause maldigestion or malabsorption in the gastrointestinal tract and subsequent nutritional compromise with assorted signs and symptoms. Furthermore, discovery of previously unrecognized exposure-related distortions continues to unfold; the mechanisms discussed in this presentation are not exhaustive. The interwoven complexity of biochemical damage and pathophysiological mechanisms makes it difficult to provide precise descriptions and classification. Just the same, we felt it to be of value to highlight the various mechanisms discussed in the literature within a workable construct, albeit imperfect.

After discussing mechanisms of metabolic harm, some of the challenges and limitations associated with research in the field of toxicology as they relate to pathobiology are presented. Finally, the relevance of this information to the clinical and public health domain is considered throughout

II. Cytotoxic mechanisms of harm

The several components and functions of the cell which can be directly or indirectly impacted by chemical toxicants will be highlighted in this section. It has long been realized that cellular toxicity can result from chemical damage at the cell membrane level where receptors and transporters are commonly found,[26, 27] at the level of various organelles (such as the nucleus, mitochondria, and/or endoplasmic reticulum), and anywhere in between in the cytosol.[28] Within the cell, chemical toxicants can also interfere with genetic material in several ways including epigenetic changes and disruption of DNA repair, signaling or chromosomal segregation.[29-32] Furthermore, interference with enzyme expression[33, 34] has the potential to impair critical pathways inside the cell, often resulting in the accumulation of biochemicals which precede the

impairment, and deficiency of requisite components distal to the impairment. The resulting disturbances of cellular homeostasis can have repercussion on other cells, tissues and organs, and ultimately on the whole organism.

Ila.... Direct Damage to Cell Structures

Some toxicants have the propensity to directly damage various cell structures including cell membranes, various organelles, as well as genetic material. Genotoxicity, for example, can be broken down into i) pre-mutagenic damage such as DNA adducts and strand breaks; ii) genetic mutations; and 3) chromosomal abnormalities such as deletions, breaks, as well as the loss or gain of a whole chromosome. It appears that assorted toxicants, including pesticides from the organophosphate, organochlorine, pyrethrin, triazine, and phenoxyherbicide families all demonstrate human genotoxic propensity with impact involving one or more of the above mentioned genotoxic modes of action.[35-39]

Among other functions, the endoplasmic reticulum (ER) within the cytosol is involved in detoxification and the synthesis, folding, and delivery of proteins. Recent evidence confirms that prolonged ER stress from toxicants such as heavy metals[40-42] and several pesticide compounds,[43-45] induces disturbance of ER homeostasis and function, including the aggregation of misfolded proteins.[46, 47] This mechanism of harm has been identified as a determinant of human illness, particularly chronic afflictions including atherosclerosis, kidney ailments, diabetes, and the formation of tumors.[46]

Extensive attention in the scientific literature has recently been devoted to mitochondria and the link between damage to these organelles and the pathogenesis of numerous chronic disease states ranging from autism[48] to cancer.[49] Myriad activities within the mitochondria are disrupted by xenobiotic agents. Vital cellular activities of mitochondria include the generation of ATP for energy production, the biosynthesis of heme, pyrimidines and sterols, calcium and iron homeostasis, as well as regulation of cell death (apoptosis) - an important defense mechanism against tumorigenesis.

Various xenochemicals can alter the transcription of mitochondrial proteins and alter mitochondrial permeability, leading to swelling and changes in calcium influx.[50] Mitochondrial injury can also lead to the production of reactive oxygen species and to consequent alteration of mitochondrial DNA,[51] which can culminate in apoptosis and various chronic illnesses (cancer, neurodegenerative diseases, cardiovascular and metabolic diseases, etc.). In addition, some toxicants can repress cellular death signaling and impair the elimination of damaged cells potentially leading to chronic inflammation.[50] Brominated flame retardants are examples of specific xenochemicals that can inflict considerable cytotoxic damage on mitochondria.[32, 33]

By these and various other cytotoxic mechanisms as will be discussed, direct damage from chemical toxicants to cell membranes and to structures within the cytosol and nucleus can disrupt human metabolism.

Iib.... Oxidative Stress

Oxidative stress refers to the corrosive and toxic impact that occurs when there is an imbalance between the production of reactive oxygen and nitrogen species and the body's ability to counteract the harmful effects of these species by antioxidants. Free radical destruction is considered to be a main pathophysiological mechanism involved in ongoing neuronal damage,[52] inflammation,[53] carcinogenesis[54], and various other pathogenic processes. Furthermore, oxidative stress is ultimately thought to be involved in the pathogenesis of many diseases including cancer, ADHD, ASD, Parkinson's, Alzheimer's, atherosclerosis, heart failure, myocardial infarction, vitiligo, and chronic fatigue syndrome.[55-67]

The overproduction of reactive oxygen and nitrogen species and the consequent oxidative stress can occur following either endogenous or exogenous insults. Exposure of the human body to various chemical agents, for example, has the potential to generate reactive species which may bind to vital components of cells, causing extensive damage to various cellular components including mitochondria, proteins, lipids and DNA.[56, 61, 68] Such radical species have the potential to disrupt many cell functions and can induce gene mutation and expression.[54] Certain

heavy metals, for instance, can mediate the formation of reactive species[69] which in turn may induce depletion of glutathione enhanced lipid peroxidation (where reactive molecules oxidize lipids in cell membranes, resulting in destruction of unsaturated fatty acids and direct damage to cell membranes), altered calcium and sulfhydryl homeostasis,[69] and various modifications to DNA bases.[55, 56, 70, 71] Nanoparticles of certain chemical agents such as titanium dioxide may also produce reactive oxygen species.[72] In addition, fungal mold organisms such as *Penicillium* and *Aspergillus* can manufacture adverse chemical metabolites called mycotoxins that have the potential to induce oxidative stress and consequent harm to human health.[73, 74]

Indirect damage of various other cell constituents can also result from products of oxidation – such as aldehydes produced from lipid peroxidation. In turn, these by-products can lead to extensive tissue damage, progression to diseases such as atherosclerosis, [55] and the production of mutagenic and carcinogenic toxins.[56, 69] It is also evident that some chemical toxicants, including various chemotherapeutic agents,[75] can potentially induce disruption of redox homeostasis – the maintenance of a physiological electrochemical potential and ionic concentration gradient across cellular boundaries. Finally, highly reactive chemical species that can adversely impact normal biochemistry can also be produced endogenously during the biotransformation of assorted xenobiotics, as the liver endeavors to metabolize and clear these toxic agents.[76]

- *Peroxynitrite (PXN)*

One reactive nitrogen species that merits particular attention and that may be formed in response to common chemical exposures such as benzene[77] as well as other toxicants[78-80] is peroxynitrite (PXN) – an oxidative and nitrative agent capable of disrupting dozens of fundamental biochemical processes and the potential to effect extensive damage to cells and tissues.[81, 82] PXN forms by the combination of nitric oxide and the toxic free radical superoxide. Somewhat of a biochemical terrorist, PXN has enormous potential to ignite biochemical havoc by inducing hydrogen abstraction (the loss of an electron located on a hydrogen atom) from essential biochemicals such as various proteins, DNA, and lipids, thus disrupting homeostasis throughout the cell.[81, 83] It is

thought by some that ongoing PXN-related destruction may be a determinant of many chronic diseases of modern civilization.[81] Research continues to elucidate the significance of PXN including its relation to other compounds such as uric acid, which appears to act as a PXN scavenger,[84] and other agents such as molecular hydrogen which may therapeutically serve to diminish PXN-related damage.[85, 86]

IIc.... Receptor Dysregulation

Essential components of physiological pathways include cell receptors that allow for the communication between various organs and cells, the orchestration of physiological responses, and the execution of specific actions within cells. Dysregulation of receptor function has been linked to various chemical toxicants and to adverse clinical outcomes.

Toxicants can alter receptor function in many ways. For example, ligands such as nutrients, hormones, and neurotransmitters may be improperly established at the receptor level leading to a diminished response - the net effect may be blockage or repression to varying degrees. Conversely, some toxicants can amplify receptor reaction and lead to an increased response (potentiation). Toxic chemicals may directly bind to the receptor or induce an immune response leading to antibody formation and antibody related alteration or sequestration of receptors.[24, 25, 87]

The literature abounds with examples of toxicant induced receptor dysregulation. For example, PCBs (polychlorinated biphenyls) and PBDEs (polybrominated diphenyl ethers) have been found to act as agonists or antagonists of thyroid receptors and alter levels of thyroxine and TSH.[25] Phthalate compounds, responsible for the varying degrees of softness in plastic items, are another example of commonly found chemicals in the environment that possess antagonist thyroid receptor activity[88] and may result in a clinically non-euthyroid state despite normal thyroid levels on blood tests. Toxicants including Hg, PCBs, as well as PBDEs and other flame retardants have been reported to be implicated in dysregulation of glutamate receptors through receptor protein potentiation.[89, 90] As the major excitatory brain neurotransmitter, glutamate enhancing effects may lead to induced neuro-excitotoxicity.

IId.... Epigenetic Alteration

Epigenetic alterations represent potentially pathological changes in gene expression or phenotype without modification to the DNA sequence itself. Epigenetic change occurs as a response to one or several environmental triggers such as toxicant exposure through gene-regulating mechanisms which include DNA methylation, histone modifications and the expression of non-coding RNA (microRNA), all affecting transcription and translation of information from the genome.[46] Some epigenetic changes serve to suppress normal gene expression, while other changes may facilitate the activation of genes.[91, 92] Recent evidence confirms that epigenetic alterations may serve as a basis for chronic illness and that such alterations can be transmitted to subsequent generations. [46, 93, 94]

DNA strands are wrapped around clusters of histones called nucleosomes forming a chain like structure called chromatin which is further arranged spatially into chromosomes. DNA methylation occurs at the level of the DNA strand at cytosine-guanosine sites (CpG) where cytosine is methylated through DNA methyltransferase into 5-methylcytosine and has the effect of suppressing gene expression.[91] Histones undergo modifications such as acylation, phosphorylation and methylation, which all influence chromatin structure and gene expression. DNA methylation and histone deacetylation repress transcription (conversion of DNA to messenger RNA); conversely, high levels of histone acetylation and low levels of DNA methylation allow access to transcription factors and allow for gene activation. On the other hand, micro RNAs, which are non-coding RNAs, negatively regulate gene expression through inhibition of translation by binding to untranslated regions of target messenger RNAs.[91, 92]

Several pollutants are known to induce epigenetic change and lead to a diseased phenotype. Global DNA hypomethylation, for example, has been reported in people who had an elevated blood level of some pesticides and persistent organic pollutants.[46] DNA methylation aberrations following exposure to dioxins has been linked to immune suppression[95] and various cancers.[96] Epigenetic modifications due to toxic metal exposure have been identified in children living in polluted areas.[97] Histone changes following exposure to neurotoxic insecticides were found to promote apoptosis and induce neurodegenerative changes.[93] Epigenetic alterations are

increasingly being linked to various other states including Parkinson's, Alzheimer's, ALS, multiple sclerosis, diabetes, and atherosclerosis, and even longevity.[93, 98]

He.... Detoxification Impairment

Among the physiological requirements for metabolic and cellular homeostasis in the human body is the elimination of intrinsic (waste products of endogenous biochemical reactions) and extrinsic (xenobiotics) chemicals. Accrual of endogenous or exogenous agents that are deleterious to cell function, can result in disrupted metabolic function and clinical illness.

Although the lipid bilayer of cell membranes is generally impermeable to hydrophilic molecules, they are permeable to thousands of lipophilic toxicants that can enter cells and cause damage to various cell constituents.[99] Cells have specific enzymes that recognize and remove intrinsic chemical wastes and nonspecific enzymes that can attach to xenobiotics to tag them with polar groups that facilitate active transport and cellular excretion.[100] The process of transforming and eliminating xenobiotic is referred to as “detoxification” and is classically divided into three biotransformation phases:[101, 102] phase 1 (bioactivation), phase 2 (conjugation) and phase 3 (elimination). (Figure 4) A main site of detoxification is the endoplasmic reticulum of the liver cell but various tissues (kidney, skin, brain, lungs, heart, testes, placenta, etc.) also participate in this biotransformation process.[103]

In Phase 1 detoxification, the lipophilic hydrocarbon is modified through oxidation, reduction or hydrolysis reactions to incorporate nucleophilic or electrophilic atoms or groups (OH-, O-, N-, S-) that will serve as attachment points in further polarizing reactions through conjugation.[103-106] Phase 1 is mainly composed of cytochrome P450 enzymes regulated by nuclear receptors,[101, 105, 107, 108] that may themselves be vulnerable to xenobiotic actions

In phase 2 detoxification, other groups such as amino acids are added through covalent bonds making the transformed xenobiotic more polar and suitable for extraction through cellular membrane transporters.[102, 109] Phase 2 involves enzymes such as methyl-transferases, sulfo-

transferases, glucuronosyl-transferases, glutathione S-transferase and reactions remain intracellular.[100, 106] The conjugated toxicants are then released into the extracellular medium where they are more easily eliminated from the body; they may also be subjected to further transformation in phase 3.[102, 110]

Phase 3 detoxification, gaining further attention in research since the discovery of permeability glycoproteins (P-gp) in 1976, involves the ATP-binding cassette (ABC) family of drug transporters. From a pharmacological perspective, such transporters are implicated in multiple drug resistance and considered a nuisance to the activity of targeted drug therapies (antibiotics, chemotherapy, etc.); but from a chemical pollutant elimination perspective, they are salvific to the cell,[102] provided they are not malfunctioning. It has been discovered that some extrinsic chemical agents can bind the P-gp and inhibit its transporter detoxifying ability. A study by Nicklisch et al. published in 2016 demonstrated inhibition of this P-gp elimination transporter by common environmental organic pollutants including some organochlorine pesticides and their metabolites, some brominated flame retardants, and various PCBs at levels commonly found in contemporary surroundings. [111]

Various chemical agents have been found to impede intrinsic detoxification pathways at one or more stages which thus impair the elimination of these and other pollutants, which in turn leads to bioaccumulation and an ever increasing body burden of contaminants with the associated physiological disruptions and toxicity.[107] For example, the ubiquitous pesticide agent glyphosate is reported to impair cytochromes P450 enzymes,[112] and lead was found to impair conjugation and elimination of some polycyclic aromatic hydrocarbons (PAHs).[113, 114] In addition, polybrominated diphenyl ethers (PBDEs) have been found to negatively modulate intracellular levels of the conjugation cofactor glutathione (GSH) while being associated with neurotoxicity of neurons and astrocytes. [115]

If.... Plaque formation

Some toxicants have been found to trigger the formation of, plaque-like structures or deposits. This section will briefly discuss the formation of alpha-synuclein, beta-amyloid and atherosclerotic plaques, which are pathognomonic of commonly seen neurodegenerative and cardiovascular diseases.

Alpha-synuclein is a protein that appears to control neurotransmitter release at the synaptic junctions of nerve cells. Increased levels and abnormal deposition of alpha-synuclein is found in Parkinson disease (PD). Alpha-synuclein is also expressed in other neurodegenerative diseases such as multiple-system atrophy, dementia with Lewy bodies, many cases of Alzheimer's disease, neurodegeneration with brain iron accumulation type I, pure autonomic failure (PAF), and even a subtype of essential tremor.[116] Although pathophysiological mechanisms are not yet fully understood, it is generally accepted that environmental exposures are an important factor in the pathogenesis of PD. Several animal and human studies have thus far have linked exposure to some pesticides, toxic elements, and solvents to an increase in alpha-synuclein deposition and some of the hallmark findings of PD.[117-121]

The histological hallmarks of Alzheimer disease (AD) are deposits of b-amyloid in the form of neurotoxic plaques. The aggregation of soluble b-amyloid forms after the peptides are cleaved from the precursor protein bound to the cell's plasma membrane. Considerable animal research has identified alterations of pathways and metabolisms associated with AD in response to certain environmental contaminants.[122] Toxicants such as brominated flame retardants (BFRs) are among the exposures potentially implicated in the pathogenesis of AD, but further studies are required to confirm causality and precise mechanisms..[122] BFRs, widespread among consumer products, are pollutants that are known for their ability to cross blood-brain barriers and bioaccumulate in humans,[123, 124] and to exhibit cytotoxic impact at low micromolar concentrations.[33] Studies on a specific line of neuronal cells, has revealed that BFRs can induce cell death through apoptosis and the activation of caspases, oxidative stress as well as the production and release of b-amyloid peptides within hours of exposure.[33] Some toxic elements

including lead, mercury, aluminum, cadmium and arsenic, some pesticides, and certain metal-based nanoparticles also have been implicated in the formation of senile/amyloid plaques.[117]

Finally, various xenobiotics such as allylamine and benzo[a]pyrene are becoming increasingly associated with vascular injury and found to be involved in the formation of atherosclerotic plaque - a critical finding in cardiovascular diseases such as hypertension, stroke, and coronary arterial disease.[125]

Ilg.... Displacement

Displacement occurs when a toxicant takes the binding spot of a nutrient or an element that is essential for the maintenance of good health in an individual. It is a specific form of receptor site competition, where the toxicant has such a high affinity for the receptor such that competition with other ligands for the receptor is virtually absent.

A well-known example of this phenomenon is carbon monoxide toxicity. Carbon monoxide is a product of incomplete combustion of carbon based compounds. Carbon monoxide is the most common type of fatal air poisoning in many countries and accounts for more than 50% of poisoning fatalities in industrial countries.[126] Carbon monoxide has a very high affinity (200-300 times that of oxygen) for hemoglobin and displaces oxygen from its binding sites on hemoglobin and produce carboxyhemoglobin. As CO binds to hemoglobin it also increases the affinity of other binding sites for oxygen leading to a left shift of the oxygen dissociation curve, thus interfering with unloading of oxygen in the tissues [127] making CO such a dangerous toxin.

Other illustrations of this phenomenon can be found with PBDEs which have been shown to displace the thyroid hormone T4 from binding proteins and as such, affect thyroid function.[25] Cadmium has also been found to displace zinc in many metallo-enzymes and at DNA-zinc binding sites.[128]

IIIh.... Other Mechanisms of Cellular Toxicity

Recent research has identified a number of other mechanisms which disrupt cellular homeostasis and which are caused, in some cases, by toxicant exposures.

- *Signalling Dysregulation*

Various toxicants have been found to impair and dysregulate normal signalling and the finely tuned turning on and off of assorted biochemical pathways.[129] Toxicants interfering with this process will potentially impair the necessary signalling for the biochemical activity to move ahead. Methylation and proper function of the intracellular methylation cycle, for example, is necessary to facilitate the proceeding of over 250 reactions within the body; hypomethylation can occur, as discussed, from exposure to various pesticide agents.[46] Another example can be seen with receptor tyrosine kinase (RTK) signaling pathways essential to the mitogenesis of progenitor nerve cells which have been found to be disrupted at environmentally relevant levels of methylmercury and lead.[130]

- *Impairment of Protein Degradation*

The Ubiquitin Proteasome Pathway (UPP) is the principal mechanism for protein catabolism in the mammalian cytosol and nucleus. This pathway is involved in a wide variety of cellular processes including antigen processing, cell division, transcription and repair, as well as biogenesis of organelles; disruption of UPP may be involved in the pathogenesis of various illnesses from dementia to cancer.[131, 132] This UPP pathway may be impacted by certain toxic elements[133] and pesticide agents.[134] [46]

- *Transporter Dysregulation*

It has also been recently identified that various toxicants have the potential to inhibit the transport of various required biochemicals necessary for metabolic processes.[111] As discussed in the detoxification impairment section, various organochlorine pesticides, BFRs, and PCBs have the propensity to paralyze cellular transport mechanisms essential for required biological processes.[111]

- *Impairment of Required Autophagy*

Autophagy is an intracellular degradation system that facilitates the breaking down of cellular components and delivers cytoplasmic constituents to the lysosome, in part for recycling. This processing appears to be instrumental for a wide variety of biological functions within the cell. Dysregulated autophagy may result with exposure to some chemical toxicants,[50, 135, 136] including various pesticides.[137, 138]

III. Pathophysiological Mechanisms of Harm

Earlier paradigms in toxicology considered a simple dose-response relationship between toxic agents and consequent damage. While this is true for some toxic agents, it has become increasingly recognized that the dysfunction underlying chronic low dose toxicity is much more complex than previously thought. Exposure to a chemical agent, for example, may not result in visible tissue injury but may impact physiological function in subtle ways that, in turn, increase susceptibility to other forms of damage.[50] In addition to various direct biochemical cellular effects that have been presented, (Figure 5) there are also a number of potential physiological alterations which can disrupt metabolic function within and outside the cell as a result of the exposure and bioaccumulation of toxic chemical agents. In this section, we will provide an overview of some of these metabolic alterations.

IIIa.... Endocrine Disruption

The field of study surrounding endocrine disruption by chemical toxicants is burgeoning.[139, 140] Endocrine disruption occurs when toxic compounds are found to act with impact on hormone receptors as mentioned, but also when they interfere with organ response and feedback loops.[46, 141, 142] (Figure 6) While some chemicals mimic endogenous hormones, others may act as blocking agents, and some interfere with hormone excretion or various transport proteins essential for the proper delivery of a hormone to its target tissue. The ultimate result can be amplification or

inhibition[46, 143] of various endocrine feedback systems with a spectrum of clinical manifestations.[139, 144] The end response is dependent on many factors, including the affinity of the toxicant to a particular receptor, the potency of the chemical, and the synergistic effect from other toxicants.[46, 143, 144] Endocrine disrupting chemicals (EDCs) have also been shown to alter gene expression, with animal work demonstrating the potential to affect several consequent generations, as previously mentioned, through epigenetic alterations.[145-147]

Many innate hormones, such as estradiol and testosterone, are bioactive at miniscule doses in parts per trillion. (Table 1) Many EDCs also have profound bioactive impact at miniscule doses.[7] While the impact of many toxicants still remains to be adequately researched, current evidence recognizes the myriad effects of hormone disruptors on several aspects of human health. Because EDCs are near ubiquitous and hormonal function affects almost every bodily function, health sequelae are numerous. EDCs can, for example, adversely affect reproductive health, thyroid and adrenal function, onset of puberty, sexual indices, and have potential impact on hormone sensitive organs such as prostate, breast, and endometrium. Table 3 provides examples of some of the ways that chemical toxicants can disrupt thyroid metabolism.[24, 25, 88, 148]

Examples from the scientific literature of the clinical and public health impact of endocrine altering agents are too numerous to recount[139, 140, 144] as many categories of compounds, such as perfluorinated compounds,[149] BPA and phthalates,[150, 151] various pesticides,[152, 153] PCBs and dioxins,[154] paraben preservatives,[155] acrylamide,[156] several mycotoxin,[157, 158] and many toxic elements such as cadmium display hormone disrupting behavior.[159, 160] EDC-related sex ratio imbalances, for example, resulting in fewer male offspring in humans have been associated with bioaccumulation of some dioxins and pesticides.[144] Phthalates and organochlorine pesticides are common toxicants that have been linked to an increased prevalence of fibroids.[144] Phthalates, PCBs, and dioxins have been associated with endometriosis.[144] Mixtures of chemicals with anti-androgenic properties, such as phthalates or a range of fungicides and pesticides during pregnancy increases the risk of cryptorchidism in the male newborn and other congenital abnormalities.[144] Recent discussion has explored the impact of endocrine disruption on gender issues, sexual preference, and sexual behavior.[161, 162] Epidemiological

evidence suggests that several groups of common contaminants, including PCBs, brominated flame retardants, phthalates, BPA and perfluorinated chemicals, are associated with decreased thyroid hormone levels in humans.[140, 163, 164] (Figure 4) The examples go on and on with emerging evidence suggesting links, perhaps by various mechanisms, between EDCs and cancers, adrenal disorders, bone disorders, and various metabolic diseases.[144] In review, the potential impact of endocrine altering hormones is vast and continues to be researched.

IIIb.... Inflammation

Toxicants can lead to inflammation in many ways: i) the release of pro-inflammatory cytokines and triggering of an immune response such as atopic illness,[165] ii) the generation and enhancement of oxidative stress, iii) direct mitochondrial and/or cellular damage, iv) toxicant mediated disruption of intracellular calcium homeostasis - which can affect various intracellular pathways and organelles, and so on.[50] Cellular signalling pathways such as the mitogen-activated protein kinase and stress-activated protein kinase cascades have also been shown to be activated and induce inflammation.[50] Phenols, polycyclic aromatic hydrocarbons (PAHs), bisphenol A (BPA), PCBs, toluene, phthalates, benzene and ethanol are among some of the chemicals found to cause inflammation through these various mechanisms.[166-171]

Dysfunctional cell survival and death pathways are also a main mechanism that toxicants employ to induce inflammation. Cellular demise mechanisms potentially inducing inflammation include autophagy, apoptosis, pyroptosis, and necrosis. Cell death in some situations can be protective (e.g. apoptosis of tumorigenic cells and elimination of genetically damaged cells) but if caused on an ongoing basis by toxicant exposure, it can be deleterious (e.g. neurodegeneration, loss of oncogenic protection and surveillance) to the organism and result in ongoing inflammation.[50] For instance, it is known that efficient phagocytosis of dead or dying cells prevents the development of inflammation during apoptosis;[172] but when cells are exposed to specific toxicants such as PCBs and certain toxic metals, autophagy or other protective cell death and recycling mechanisms become dysregulated[173, 174] and inflammation may no longer avoided.[50]

Over the last decade, research related to the emerging production of nanoparticles has spawned the field of nanotoxicology.[175] Some nanoparticles, for example, have been found to induce autophagy, apoptosis or necrosis and produce reactive oxygen species (ROS) leading to increased oxidative stress and inflammation.[176]

IIIc.... Immune Dysfunction

The immune system is a complex interactive network of lymphoid organs, specialized defence cells imbedded in various tissues, as well as humoral factors and cytokines. Its function is, in part, to defend the body from infections and tumors.[177] Environmental pollutants such as heavy metals, solvents, and pesticides have been shown to dysregulate the immune system potentially resulting in immune suppression, auto-immune conditions and/or hypersensitivity states.[178]

- *Immune Suppression*

By various ways including suppression of natural killer cells, dysfunction of T-cells and so on, various chemical agents including heavy metals and commonly used pesticides have been found to suppress immune system cells and could possibly impair immune function in vivo. For example, the toxic element mercury, as well as various pesticide groups including organophosphates, triazines (atrazine) and carbamates induce a significant dose-dependent decrease in the performance of human T and natural killer lymphocytes which are vital in the immune **defence** against tumors and viruses.[179-181] Impaired immune competence via suppressed cell mediated immunity, reduced T cell count, and downregulation of phagocytic activity of lymphocytes was also a common finding following the 1984 Bhopal industrial catastrophe in India where about a half million people were exposed to various toxins released by a pesticide plant.[182-184]

- *Autoimmunity*

Increasing research has begun to suggest that chemical exposure can produce autoimmune manifestations in human populations and promote the development of autoimmunity.[20, 185, 186] Human and animal research has confirmed the link between chemical exposure and autoimmune pathology for agents including solvents [186] such as trichloroethylene,[104, 187]

some pesticides such as hexachlorobenzene,[188, 189] various inorganic metals,[190-192] and other exposures including silica[193] and asbestos,[194] In mice experimentation with trichloroethylene, for example, it was observed that while T-lymphocytes were activated along with increased production of IFN-gamma, pro-inflammatory cytokines were released with a corresponding inhibition of T cell apoptosis.[195] With the protective and suppressing process of apoptosis deleted, autoimmunity was promoted and confirmed by the presence of autoantibodies and pathological evidence of autoimmune hepatitis.

In epidemiologic study of human populations, certain demographic determinants such as proximity to industrial regions appears to be associated with rates of autoimmune diseases; clusters of autoimmune illness tend to accompany adverse exposures in population groups. For example, pneumoconiosis and scleroderma are seen in workers exposed to crystalline silica whereas scleroderma and Raynaud's phenomenon are seen in vinyl chloride workers.[196-199] Smokers have also been found to be at higher risk of seropositive rheumatoid arthritis.[186]

Further study is required to better understand precise mechanisms potentially involved between toxicant exposures and the development of many autoimmune conditions, but it has been hypothesized by some that cells and tissues which retain toxic chemical agents following an adverse exposure present differently to an intact immune system and trigger an autoimmune response. Nonetheless, increasing evidence through in vitro studies, animal and human epidemiological studies supports the proposition that chemical agents including mercury, iodine, vinyl chloride, certain pharmaceuticals, solvents, hydrocarbons (benzene, toluene, ethylbenzene, xylene, pristane, phytane) and crystalline silica are determinants of autoimmune diseases.[185, 196, 197, 200-202]

- *Loss of Tolerance / Hypersensitivity*

Recent evidence has also linked toxicant exposure and bioaccumulation with the pathogenesis of various hypersensitivity states.[178] Whether considering such reactions in the form of classic atopic diseases (allergies, asthma, eczema) or more complex presentations with extensive multi-morbidity – given diagnostic labels such as ‘environmental sensitivities’, ‘multiple chemical

sensitivity' (MCS), or 'sensitivity related illness'(SRI) - these presentations have become more prevalent as the world has produced and released more chemical pollutants.[178, 203]

Evidence increasingly suggests that such conditions may be immune-related through a mechanism called TILT or a toxicant induced loss of tolerance.[178, 203, 204] The TILT model, first described by Miller[204] (Figure 7), illustrates the link between toxicants, the immune system and symptoms. In 2010, De Luca and team found that MCS patients produced high levels of IFN-gamma, IL-8, IL-10, and VEGF with lower levels of glutathione S-transferase and glutathione when compared to control populations.[205] Emerging research on this SRI state confirms that elevated nitrotyrosine (a peroxynitrite marker) is a potential disease biomarker for this condition[206] - a finding which provides clues as to the pathological metabolic dysfunction that characterizes this hypersensitivity state. Reduction of the total body load of toxicants foreign to the body has been associated with resolution of the SRI state and normalization of tolerance.[178]

Other studies have found correlations between pediatric allergies and prenatal exposure to toxicants through vertical transmission,[207, 208] the latter being an increasingly common observation in perinatal medicine.[2, 209] While elevations in IgE were correlated with organochloride placental contamination,[208] respiratory symptoms in the newborn were observed with prenatal maternal exposures to polycyclic aromatic hydrocarbons (PAHs), PCBs and dioxins[210, 211] and **allergies were triggered** in children of mothers exposed to marine pollutants, lead, PFCs and dioxin-like compounds.[207, 212-214] Hypersensitivity was also a common and enduring finding two decades later among children born of mothers exposed in the Bhopal tragedy.[215]

In addition to the metabolic changes as a result of immune system dysregulation, there are various secondary effects of an atopic hypersensitive state. For example, as a result of contamination with certain chemical pollutants including arsenic and lead,[216, 217] IgE elevation and mast cell degranulation often occur with release of histamine when triggered. As a bioactive amine, histamine can have profound metabolic effects with clinical symptoms in some individuals.[218, 219]

III d Pathway Dysregulation

Disruption of metabolic pathways through enzyme dysregulation can induce a cascade of pathophysiological effects as a result of the accrual of biochemicals prior to the site of pathway disruption and deficiency of required components distal to the position of the affected enzyme. Genes provide the template or recipe for the coding of enzymes required for the myriad physiological pathways in the body. A simple but critical malfunction or interruption of a cellular pathway by disrupting the production or function of a required enzyme can have major consequences on the macroscopic functioning of the organism and can manifest as clinical symptoms and disease.[29, 107] This section will highlight the importance of enzymes as a major target of toxicants and a key element to the integrity of cellular and biochemical pathways that take place anywhere within a cell and its organelles or in an extracellular compartment.

Many examples of pathway dysregulation are discussed in the literature. Heavy metals have been found to impair the function of many enzymes and to disrupt fundamental intracellular pathways in numerous ways.[220] Mercury, for example, has the potential to impair glutamic acid decarboxylase (GAD)[220] an enzyme that catalyzes the decarboxylation of glutamate to GABA – leading to accumulation of the excitatory neurotransmitter glutamate, while diminishing the production of the relaxing neurotransmitter GABA. Mercury also has the potential to disrupt the basic process of methylation in cells,[220] required for over 150 metabolic processes including DNA repair, genetic expression, production of some neurotransmitters, and so on.[221, 222] Cadmium and arsenic have been shown to stimulate mitogen-activated protein kinase phosphorylation.[223] The enzymatic pathway for proper tetrahydrobiopterin metabolism, crucial for the production of several neurotransmitters including serotonin, dopamine and norepinephrine, is impaired in the cell by the presence of common contaminants including aluminum[224] and lead.[225] Another important example of enzymatic distortion with profound potential consequence is the impact of lead on nitric oxide synthase (NOS) activity.[226] Lead contamination can interfere with the production of nitric oxide,[227] impairing proper blood circulation and unleashing the consequent production of radical oxygen species superoxide as a result of NOS uncoupling.

Other types of toxicants are also potent enzyme dysregulators. In a study exploring the effect of maternal smoking on the expression of metabolic enzymes in human fetal liver, O'Shaughnessy et al. were able to demonstrate that fetuses exposed to toxicants displayed a significantly altered expression of mRNA transcripts for liver enzymes.[34] Animals exposed to PCBs have also demonstrated decreased levels of the enzyme GAD and manifested audiogenic seizures.[228] PCBs have also been found to interfere with the TLR4/NF-kB pathway and enzymes (such as nitric oxide synthase) in a way that results in an impairment of immune response and macrophage responsiveness.[229]

To review: within each pathway, substrate A makes product B. For this to occur, gene function to produce enzyme 'AB-ase' must be in order and operational, the required nutrient cofactors to facilitate enzyme action must be present, and the absence of toxicant dampers must be secured. Disruption of metabolic pathways by genetic compromise, enzyme damage, deficiency of required cofactors, or activity of toxic agents may paralyze the normal biochemistry of the body and result in clinical illness. While much attention of late has been extended to SNPs (single nucleotide polymorphisms) variants that impair the full potential of the enzyme to carry out the metabolic process from A to B, there is insufficient awareness that many toxicants are dysregulating enzymes and interfering with pathway progression.

IIIe.... Biome Alteration

The human biome refers to the body's ecosystem of microscopic organisms residing in many locations including the skin, female vagina, sinuses, and most abundantly in the gastrointestinal tract.[230, 231] This biome includes various types of organisms including viruses, helminths, prokaryotes and eukaryotes.[232, 233] These organisms play a major role in metabolic homeostasis and individual health with functions including the release of neurotransmitters, proper digestion and absorption of foodstuffs, production of required nutrients (e.g. vitamin B12, vitamin K2), modulation of the immune system, detoxification, and so on. A healthy gut biome also provides protection against microbial overgrowth and dysbiosis and conversely, an unhealthy biome has been associated with various disease processes.[234] The importance of the biome as a

determinant of health is so significant that some authors refer to it as ‘the 11th organ system’. [230, 235]

Common environmental chemicals (such as chlorine, heavy metals, assorted pesticides, antibiotics, etc.) are found to interfere with microbiome viability and functionality – with potentially adverse clinical outcomes.[112, 236-239] Differences in microbiota species, diversity and distribution, for example, are extensively described in inflammatory bowel disease.[240, 241] The loss of the beneficial oxalate metabolizing bacteria ‘*Oxalobacter formigenes*’ is a particular example of microbiome damage where the breakdown of oxalates becomes significantly reduced, leading to increased oxalic acid absorption and bioaccumulation of oxalate.[242] Elevated oxalates may have deleterious consequences which include mitochondrial damage, generation of reactive oxygen species, oxidative stress, repression of cellular respiration (TCA cycle), **and** reduction in antioxidant enzymes and glutathione.[243, 244] High oxalate levels contribute to cellular dysregulation and malfunction, which may further translate into clinical manifestations and disease,[245] such as nephrolithiasis[246] and mental health issues including autism.[242]

A fundamental realization relating to biome alterations has been the recognition that the ability to effectively eliminate toxic compounds requires a healthy, functioning biome.[247] Accordingly, concerted efforts are being explored to prevent biome damage in the early stages of life,[248] and to restore biome health throughout life. Interventions to restore the microbiome include the use of pre and pro-biotics, the adoption of fermented foods in the diet and fecal implants. For instance, it was found that the most efficacious treatment for *Clostridium difficile* colitis was fecal bacteriotherapy.[249, 250] However, sustained improvement and adequate colonization of the biome would necessitate addressing the adverse and ongoing impact of adverse exposure and the underlying accumulated toxicant burden in order to preclude ongoing destruction of healthy organisms.[112, 236, 251]

III f.... Autonomic Nervous System Dysregulation

The Autonomic Nervous System (ANS) is the neurological regulatory system for many automatic functions in the body. It controls breathing, heart rate, gastrointestinal function and motility, vasodilatation, thermoregulation, papillary function, and so on. Malfunction of the ANS can thus lead to a myriad of clinical manifestations such as arrhythmias, orthostatic hypotension, constipation or diarrhoea, vasomotor symptoms, alterations in blood pressure and various other abnormal clinical states. ANS dysfunctions can therefore have significant impact on health and wellbeing and, at times, be associated with fatal events.

Various adverse chemicals can impact the ANS, either in excitatory or inhibitory ways. For example, some xenobiotics, such as assorted chemical warfare agents,[252] may act as relative cholinergic blockers, which block the action of cholinergic nerves that transmit impulses by the release of acetylcholine at their synapses, thus paralyzing the proper function of the autonomic nervous system. In occupational settings, carbon disulfide (CS₂), lead (Pb) and excess manganese (Mn) have been found to have toxic effects on the ANS, inducing neurobehavioral, neuroendocrine (affecting acetylcholine, dopamine, noradrenaline and serotonin neuronal conduction) and neuromuscular abnormalities.[253]

Impairment of cardiac autonomic function and diminished heart rate variability (HRV) has been observed in response to certain toxicant exposures and has sometimes been used as a marker for ANS activity and integrity. Nicotine, smoke inhalation, and organic solvents, for example (such as n-hexane, xylene and toluene) have been observed to affect the cardiovascular system and diminish heart rate variability.[253, 254] Exposure to particulate matter, a common event in polluted areas, has also been associated with ANS changes and increased arrhythmogenicity.[255] Reduction of HRV, a predictor for increased risk of cardiovascular morbidity and mortality, has also been demonstrated to correlate with exposure to higher levels of particulate matter.[255]

IIIg.... Neurotransmission Dysfunction

Neurotransmitters are endogenous chemicals that enable neurons to transmit signals across their synaptic junctions to message other neurons or target cells (muscles, glands, etc.). Neurotransmitters are vital to the organism at a microscopic and macroscopic level and for voluntary and involuntary actions. Common neurotransmitters include glutamate, gamma-aminobutyric acid (GABA), glycine, serine, acetylcholine, dopamine, noradrenaline, epinephrine, serotonin, melatonin, histamine, vasopressin, gastrin, secretin, motilin, somatostatin, nitric oxide, and adenosine.

GABA for example, is a chief inhibitory neurotransmitter in the central nervous system (CNS). It is synthesised from the excitatory neurotransmitter glutamate and plays an important role in regulating neuronal excitability. The release of GABA into the synapse depends on its synthesis, loading into vesicles, its reuptake, transformation rate back into glutamate, and other indirect factors.[256] GABAergic malfunction has been associated with epilepsy, cognitive impairment, anxiety, neurodevelopmental disorders and ASD.[256] Various toxicants such as PCBs and PBDEs, heavy metals such as mercury and lead, and various other adverse agents can impair GABA receptors and lead to neuronal excitability.[143, 257, 258] For example, it has been found that PCB-47 and the brominated flame retardant metabolite 6-OH-PBDE-47 act as agonists on inhibitory GABA(A)-mediated signaling and excitatory $\alpha(4)\beta(2)$ nACh-mediated signaling pathways.[143]

Furthermore, glutamate is the most abundant and the major excitatory brain neurotransmitter. It influences a range of important cognitive and motor functions including learning, memory and behavior control.[89] Various toxicants including PBDEs, PCBs, and Hg impact glutamate physiology by dysregulating its uptake at the synaptic level, leading to potentiation of its effect on receptor proteins and resulting in excito-toxicity.[89, 90]

IIIh. ...Nutritional Compromise

Some toxicants provide interference with absorption, assimilation and/or utilization of nutrients. This can occur through different mechanisms including biome disruption, enzyme dysregulation, gastric inflammation, and so on. As a consequence, individuals may be rendered nutritionally compromised and their ability to clear toxins and perform physiological functions becomes negatively affected. For example, tobacco is associated with diminished levels of zinc, beta carotene, folic acid (Vitamin B9), vitamins B6, C, and E.[259]

Cadmium, a toxic element commonly found in vehicle emissions, decreases the intestinal absorption of calcium and directly interferes with the incorporation of calcium into cells, it interferes with parathyroid hormone stimulation of vitamin D production in kidney cells, it reduces the activity of kidney enzymes activating vitamin D, and it increases excretion of calcium through the urine.[260] Cadmium can also contribute to zinc deficiency.[128] Accordingly, this toxic metal can be associated with nutritional compromise in many ways.

Medications are a special example of xenobiotics that can be found to be a causative factor in nutritional deficiency or insufficiency states. Some may lead to a vast spectrum of possible deficiencies either by directly inhibiting absorption, or indirectly through the modification of the gastrointestinal biome (e.g. antibiotics). Table 4 provides a brief overview of some commonly prescribed medications and the deficiencies that are potentially associated with these agents.[261]

IIIi Other Emerging Mechanisms of Pathophysiological harm

- *Degranulation Dysregulation*

Another intriguing pathophysiological process potentially related to toxicant exposure is the dysregulation of degranulation from specific cells including mast cells, basophils and eosinophils. There has been increasing attention to the issue of inflammatory mediators from mast cells, for instance, as a determinant of various chronic illnesses. [262-268] Mastocytosis [262, 269] and

mast cell activation [270, 271] appear to be mechanisms associated with the inexplicable release of elevated levels of inflammatory mediators from mast cells. One bioactive substance from mast cells, histamine, is involved in many physiological processes including regulating gut function, facilitating immune processes, triggering inflammatory responses, acting as a neurotransmitter, and as a mediator of pruritus; altered histamine release may affect various physiological roles. Although much research remains to be done to understand the precise pathogenesis of conditions associated with mast cell dysregulation, it has been recently found that disruption of proper mast cell degranulation may be generated by toxic agents including mercury.[272, 273] arsenic,[274] some pesticides,[275] phthalates,[276] bisphenol A,[277] as well as some mold and mycotoxin exposures.[278, 279]

IV. Limitations

While extensive ongoing study is underway to delineate metabolic and health effects associated with specific toxicants, such research is limited by particular challenges associated with human toxicology research.

- *Toxicokinetic uncertainty*

There is limited available research in certain aspects of clinical biochemistry related to toxicants including i) excretion pathways for some compounds, ii) outcomes of interaction between many toxicants and inherent biochemistry, iii) synergy and interaction between assorted xenobiotic compounds, and iv) toxico-kinetic behavior for many of the chemical agents currently in our environment. As a result, a primary problem with human toxicant research is that bioactive mechanisms of impact for some chemical agents are still not well understood. Furthermore, because of the multiplicity of exposures experienced by most individuals today, it is difficult to attribute specific outcomes to a particular exposure.

- *Lack of high level evidence*

It is not possible to do prospective clinical trials on the health and metabolic effects of exposures on humans as it is unethical to expose individuals or groups to potentially toxic compounds in order to study their biochemical or physiological response – accordingly animal studies and less reliable human observational studies are used instead. Such studies are much more likely to be affected by confounding variables, such as the metabolic impact from the concomitant presence of other toxicants.

- *Chemical sequestration*

Quantifying metabolic impact at specific toxicant blood or urine levels is of limited value as biomonitoring values are notoriously inaccurate. Many chemicals that sequester in tissues are not necessarily present in blood, and many are not excreted into urine. Levels measured in peripheral blood or urine on a single occasion only represent a ‘snapshot’ that may not reflect the actual degree of contamination. Furthermore, serum levels of xenobiotics may fluctuate due to movement in and out of cells depending on various factors including exercise and caloric intake.[280]

- *Genomic Variability & Chemical Interaction*

Confounders can also make it difficult to interpret the results of toxicant exposure outcome studies. Each individual, for example, has a unique genome and may respond differently to toxic exposures. It is thus not possible to extrapolate findings from individuals to larger groups. Synergy or interaction between various chemical compounds may also alter the impact of any individual agent. With the array of combinations and permutations of potential exposures continuing to unfold at an unprecedented rate, the reality is that there is a paucity of credible data on the precise metabolic impact of bioaccumulation for each individual compound or for collective chemical cocktails.

In review, challenges remain when attempting to conclusively quantify the full metabolic impact of chemical exposures. Nonetheless, this paper has tried to provide an overview of biochemical

and physiological alterations identified to date as a result of toxicant exposure and accrual. As a consequence of these and other potential metabolic alterations, ongoing research continues to elucidate the clinical impact that such agents are having on human health.

Increasing numbers of Public Health and Toxicology journals have focused on illuminating the outcomes of such research. What is clear is that low level exposure to, and/or accrual of selected chemical compounds appears to increase the risk for potentially serious clinical sequelae including cancer,[281] reproductive dysfunction,[282] endocrine dysregulation,[283] immune alteration,[284] congenital anomalies,[285] as well as neurological and psychiatric dysfunction.[286] In response to this unfolding research, increasing exploration of interventions and strategies to facilitate elimination of bioaccumulative toxicants is underway in order to preclude the looming damage associated with toxicant accrual.[5, 22, 287-291]

V. Concluding Thoughts

The human body is a biochemical factory, continually making what it needs to function and to maintain homeostasis. Physiologically, the functioning of this intricate organism represents the sum total of metabolic pathways – if these pathways malfunction microscopically, the body malfunctions macroscopically, leading to morbidity and mortality. As discussed in this paper, various chemical agents have been shown to disrupt biochemistry and physiology in many ways, potentially resulting in varying degrees of metabolic error. With widespread bioaccumulation of numerous assorted chemicals in many population groups,[1, 2, 4] the ensuing metabolic disruption is not without consequence for individual and global health – a reality that is now ineluctable.



Table 1 – Examples of physiologically active levels for some common hormones, toxicants, and pharmacological compounds for comparative purposes.[9, 292-299]

Uric acid (serum) reference range for adult males is 3.7-8.0 mg/dL (220-476 micromole/L) and 2.7-6.1 mg/dL for women (160-363 micromole/L). Conversion factors between the different concentration units are as follow: 1 ng/dL = 0.01 ppb, 1 ng/mL = 1 ppb. It is considered that 1 L of water (or serum) corresponds to 1000 g of water. It follows then that 1 L of water represents 55.51 moles of water. Therefore, 1 pmol of a compound/L of water (or serum) corresponds to 1 pmol of compound / 55.51 moles H₂O or simply 0.0180 pmol of compound/mol of water (or serum).

Active Compound	Concentration Levels				Effects on Human Body
	Mass/volume	In ppb based on mass fractions	Molar	In ppb based on molar fractions	
HORMONES					
Endogenous Free Estradiol, Serum					
Adult Males	0.2 – 1.5 pg/mL	0.0002 – 0.0015			Reproductive functions & development
Adult Females	0.6 – 7.1 pg/mL	0.0006 – 0.0071			Reproductive functions & development
Endogenous Estradiol, Serum					
Adult Males	8.0 – 35 pg/mL	0.0080 – 0.0350	< 224 pmol/L	< 0.0000040	Reproductive functions & development
Adult Females (follicular)	30 – 100 pg/mL	0.0300 – 0.1000	60 – 854 pmol/L	0.0000011 – 0.0000154	Reproductive functions & development
Adult Females (Luteal)	70 – 300 pg/mL	0.0700 – 0.3000	82 – 1251 pmol/L	0.0000015 – 0.0000225	Reproductive functions & development
Adult Females (Postmenopausal)	< 15 pg/mL	< 0.0150	< 202 pmol/L	< 0.0000036	Reproductive functions & development
Endogenous Free Testosterone					
Males 1-8 years	< 0.04 – 0.11 ng/dL	< 0.0004 – 0.0011			Reproductive functions & development
Males 20-25 years	5.25 – 20.7 ng/dL	0.0525 – 0.2070			Reproductive functions & development
Females 20-25 years	0.06 – 1.08 ng/dL	0.0006 – 0.0108			Reproductive functions & development
DRUGS					
Albuterol	25.0 ng/mL	25			Asthma treatment; improves FEV1 albeit with an associated increase in heart rate
Carbamazepine					Anti-convulsive action
- Free serum (critical)	> 4,000 ng/mL	> 4000			
- levels found in treated water (Ottawa, Canada)	0.0003 ng/mL	0.0003			
Cialis	30 ng/mL	30			Used in the treatment of erectile dysfunction
Ethinyl Estradiol					Reproductive functions control
- 1-hour post single 20 microgram dose	29 – 58 pg/mL	0.029 – 0.058			
Metformin (glucophage)					Glycemic control
- therapeutic range	1 – 2 mcg/mL	1000 – 2000			
- levels found in treated water (Ottawa, Canada)	13.9 ng/L	0.0139			
Paxil	30-120 ng/mL	30 – 120			Antidepressant
Phenytoin					Anti-convulsive action
- Free (critical)	> 2.5 mcg/mL	2500			
- Total (critical)	> 30 mcg/mL	2500			
Vancomycin (target trough levels)	10.0 – 20.0 mcg/mL	10,000 – 20,000			Antibiotic
TOXICANTS					
PFCS (found in stain resistance treatment applied to clothes, furniture & carpets as well as antiadhesive coatings)					
Median serum levels in the USA					
PFOA	4 ng/mL	4	0.024 micromoles/L	0.43 ppb	Used as controls
PFOS	21 ng/mL	21	0.130 micromoles/L	2.34 ppb	Used as controls
Levels found in people who lived at least for 1 year in an area contaminated with PFCS (PFOA levels ≥ 0.05 ng/mL)					
PFOA	350 ng/mL	350	2.1 micromoles/L	38 ppb	Significant changes in uric acid levels
PFOS	50 ng/mL	50	0.3 micromoles/L	5.4 ppb	Significant changes in serum uric acid levels (+ 0.2-0.3 mg/dL or + 12-18 micromoles/L)
BisGMA (resin monomer typically used in dental restorations)			0.1 mmol/L	1,800 ppb	Extreme depletion of glutathione and apoptosis of human gingival fibroblasts

**Table 2. Mechanisms of Metabolic Harm:
Classification of Biochemical and Pathophysiological Alterations**

CELLULAR TOXICITY	PATHOPHYSIOLOGY
Damage to Cell Structures (e.g. DNA)	Endocrine Disruption
Oxidative Stress	Inflammation
Receptor and Transporter Dysregulation	Immune Dysfunction
Epigenetic Change	Pathway Dysregulation
Cellular Detoxification Impairment	Biome Alteration
Dysregulation of Signalling	ANS Dysregulation
Plaque Formation	Neurotransmission Dysfunction
Displacement	Nutritional Compromise
Other Mechanisms of Cellular Toxicity	Other Mechanisms of Pathophysiological harm

Table 3. Example of Endocrine Disruption: Some of the many ways toxicants can disrupt thyroid metabolism [24, 25, 88, 148]

BPA and phthalates	—————>	Binds thyroid hormone receptors
DDT & PCBs,	—————>	Bind TSH receptor
PBDEs & Triclosan	—————>	Induction of thyroid autoantibodies
Phthalates	—————>	Blocks Iodide uptake
PCBs,	—————>	Binds thyroid transport protein
Fungicide (Mancozeb)	—————>	Impairs thyroid hormone production
Toxic Metals (Pb, Hg, Cd, etc)	—————>	Inhibition of Deodinases
Organochlorines	—————>	Direct Thyrotoxicity

Table 4. Medications and the Associated Deficiencies that May Occur

Drug or type of drug	Possible deficiency
Antacids	Folic acid, Calcium, Copper, Phosphate, Vitamin A, Vitamin B ₁₂
Antibiotics	Vitamin K, L-leucine, Biotin
Atorvastatin	Coenzyme Q ₁₀
Beta-adrenergic blocking agents	Coenzyme Q ₁₀
Bile acid sequestrants	Calcium, Carotenoids, Folic acid, Vitamins A, D, E, K, Zinc
Bisacodyl (Dulcolax, stimulant laxative)	Potassium
Chemotherapy	Magnesium, Vitamin B ₂ , Taurine, and many other nutrients
Cholestyramine	Carotenoids, Fat, Folic acid, Calcium, Iron, Magnesium, Phosphorus, Zinc, Vitamin A, Vitamin B ₁₂ , Vitamins A, D, E, K
Conjugated oestrogens (Premarin)	Vitamin B ₆
Corticosteroids	Calcium, DHEA, Magnesium, Melatonin, Potassium, Folic acid, Vitamin B ₆ , B ₁₂ , C, D, K, E, Selenium, Zinc
Digitalis (Digoxin, Lanoxin, Digitoxin)	Magnesium, Calcium, Sodium, Potassium
Diuretics	Magnesium, Potassium, Zinc, Vitamin B ₁
L-dopa (Levodopa, Dopar, Larodapa)	Vitamin B ₆ , Potassium
Edetate calcium disodium (EDTA)	Calcium, Zinc
Furosemide (Frusemide, loop diuretic)	Calcium, Magnesium, Potassium, Vitamin B ₁ , Vitamins B ₆ and C
Heparin	Vitamin D
Histamine H ₂ -antagonists	Iron, Zinc, Folic acid, Vitamin B ₁₂
Isoniazid (INH, Laniazid, Rifamate, Rimactane)	Calcium, Folic acid, Magnesium, Vitamins B ₃ , B ₆ , B ₁₂ , D, E, K
Losartan (Cozaar, angiotensin-II receptor antagonist)	Calcium, Chloride, Magnesium, Potassium, Sodium, Phosphate
Metformin (Glucophage)	Vitamin B ₉ , B ₁₂
Methotrexate	Calcium, Vitamin B ₉
Oral contraceptives	Magnesium, Manganese, Zinc, Folic acid, Vitamins B ₁ , B ₂ , B ₃ , B ₆ , B ₁₂ , C
Proton Pump Inhibitors	Beta carotene, Vitamin B ₁₂ , Calcium
Simvastatin (Zocor)	Coenzyme Q ₁₀ , Vitamin E, Beta carotene
Thiazide diuretics	Magnesium, Potassium, Sodium, Zinc
Ventolin (Albuterol/Salbutamol/Proventil)	Calcium, Magnesium, Phosphate, Potassium

Figure 1 – Environmental contamination.

(NO_x = Nitrogen oxide compounds; SO_x = Sulfur Oxide compounds)

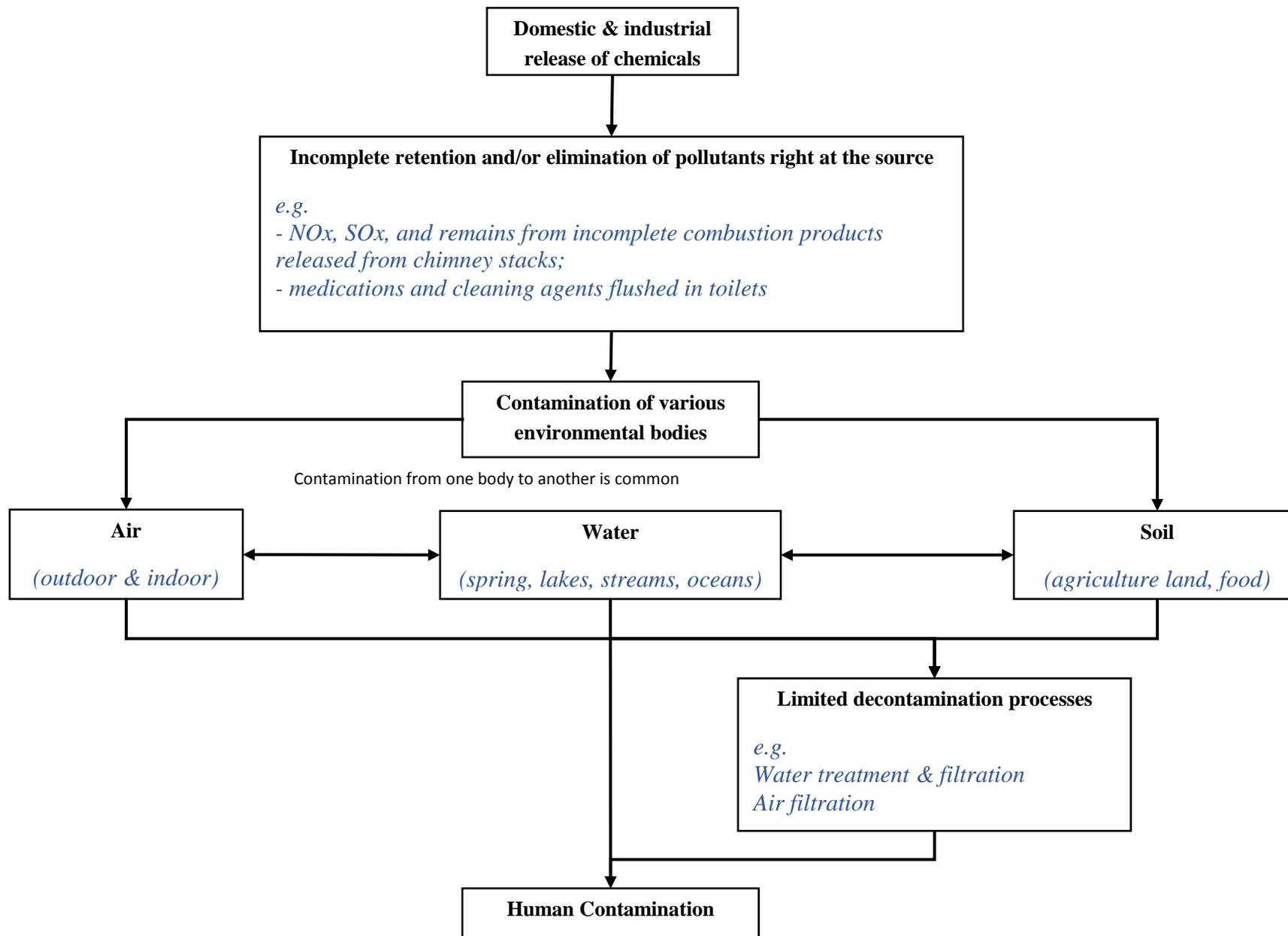


Figure 2 – Overview of exogenous toxicant passage from the environment through the human body.

(Body wastes are not included.)

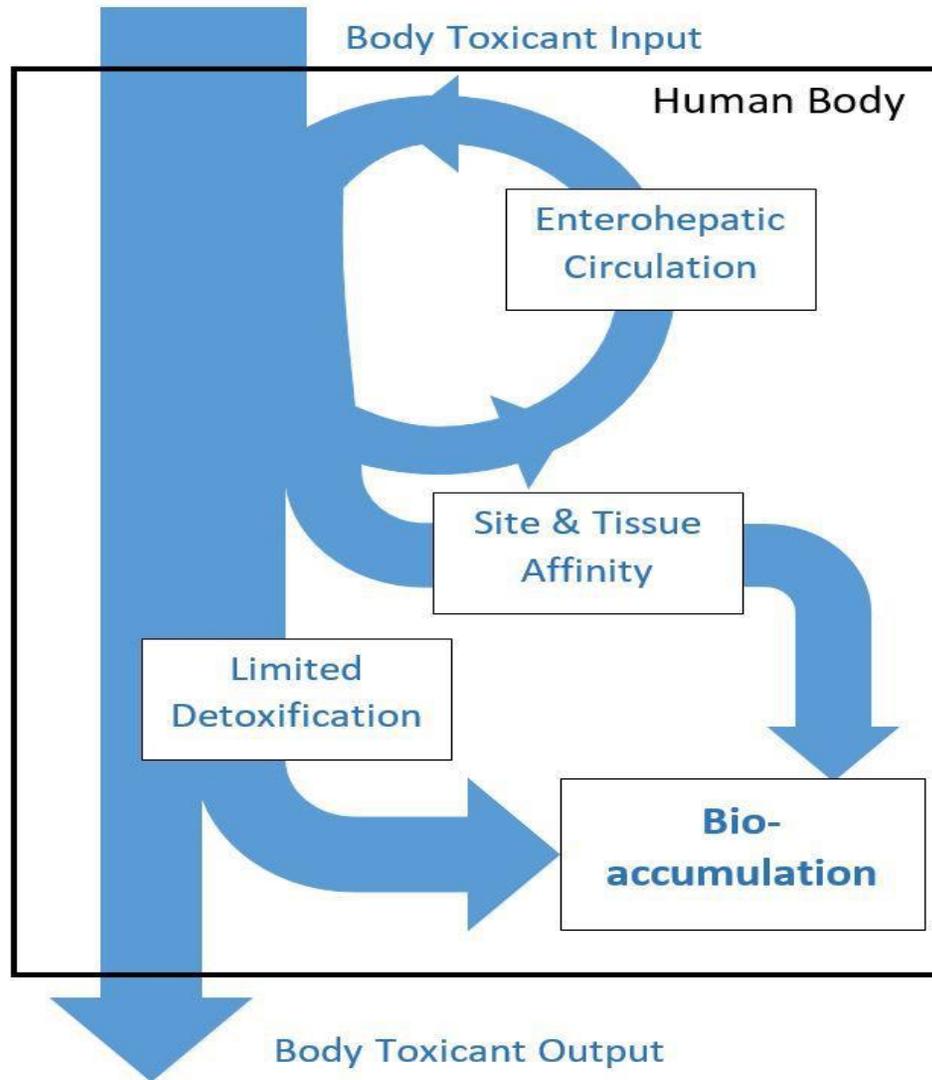


Figure 3 – Pathway to clinical disease.

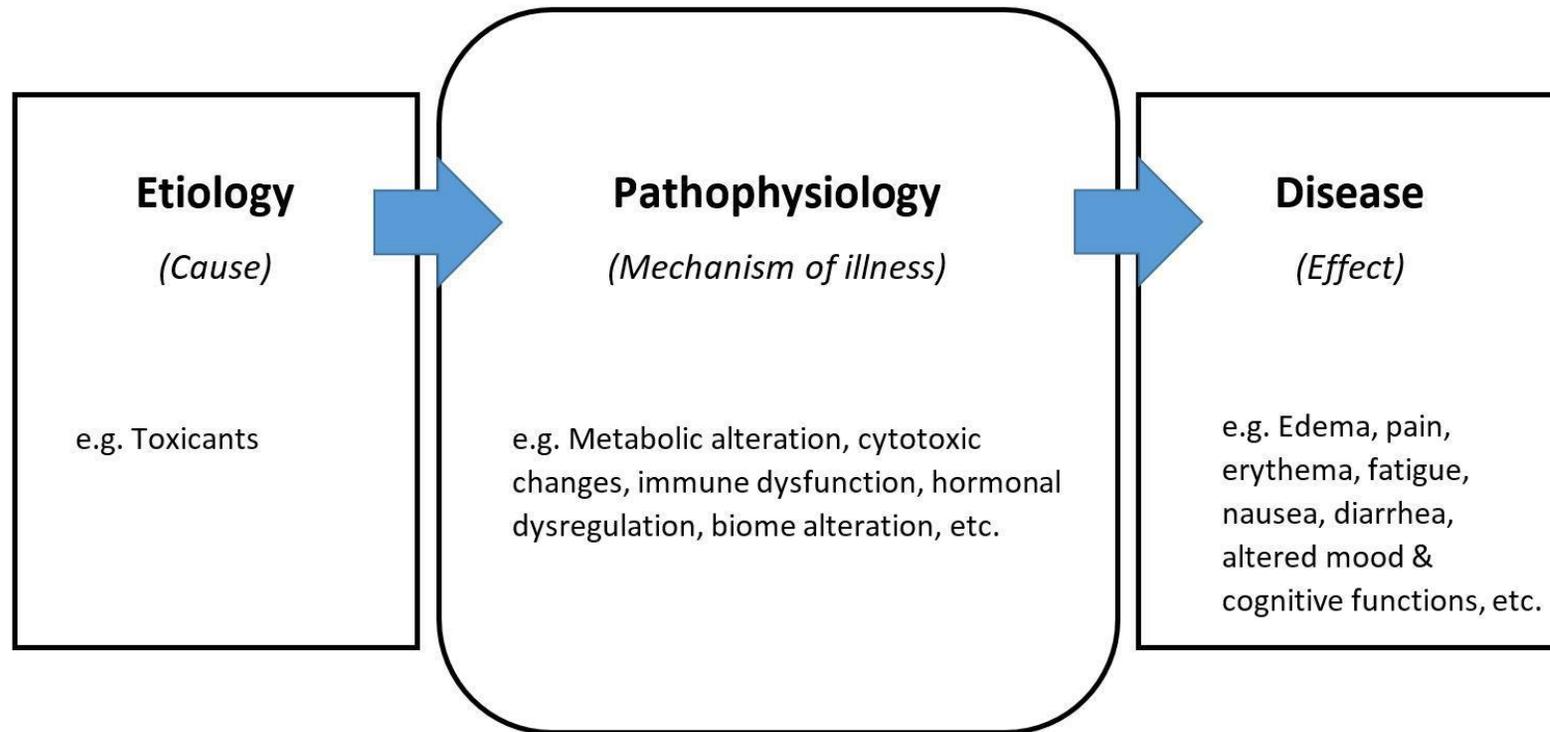


Figure 4 – Simplified overview of the main steps involved in the elimination of intrinsic waste products of metabolism, xenobiotics and toxicants.

(Dashed lines represent short cuts that some compounds may take).

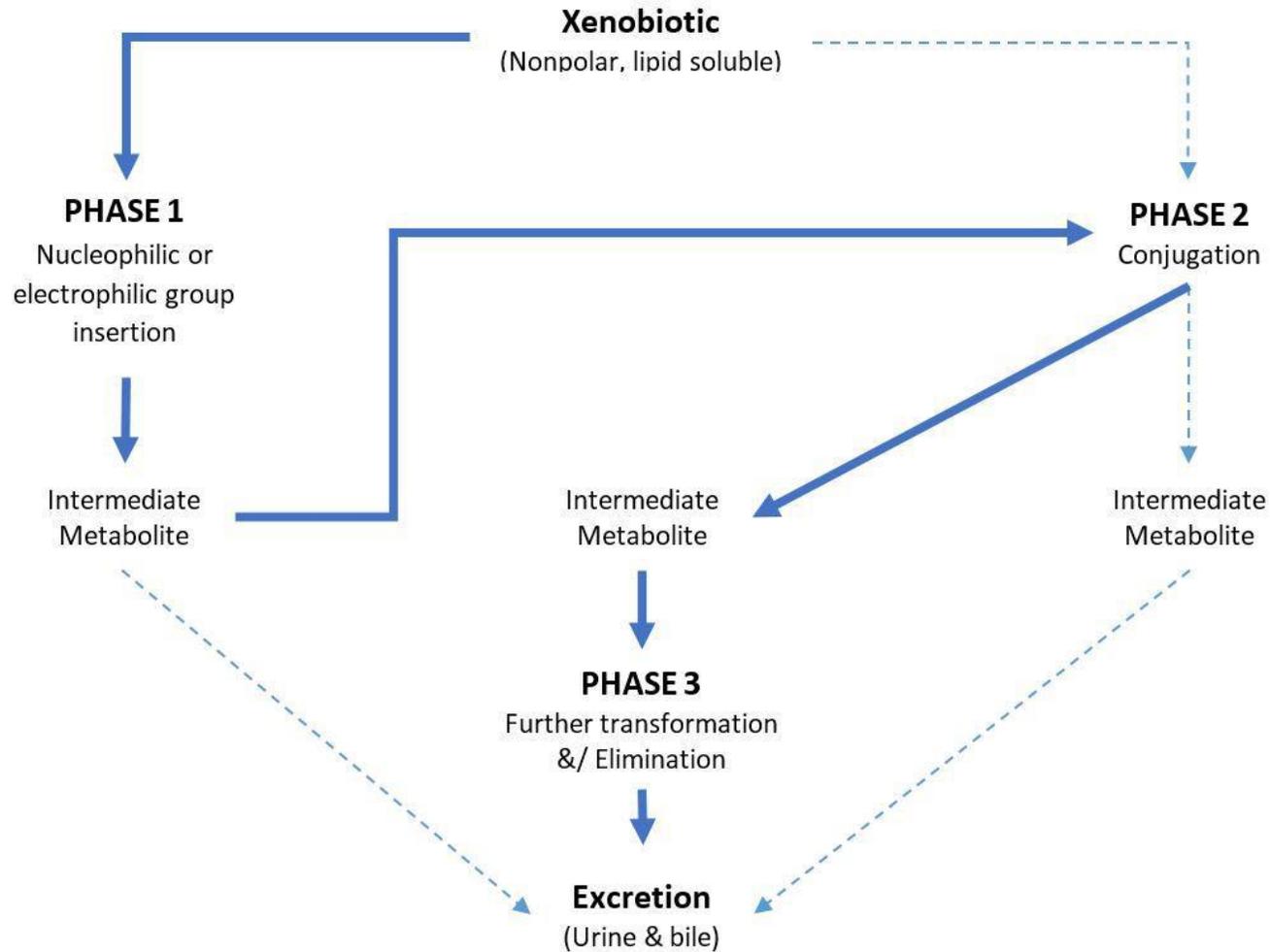


Figure 5 – Simplified overview of main mechanisms of cellular and extracellular toxicity.
(ER = Endoplasmic reticulum)

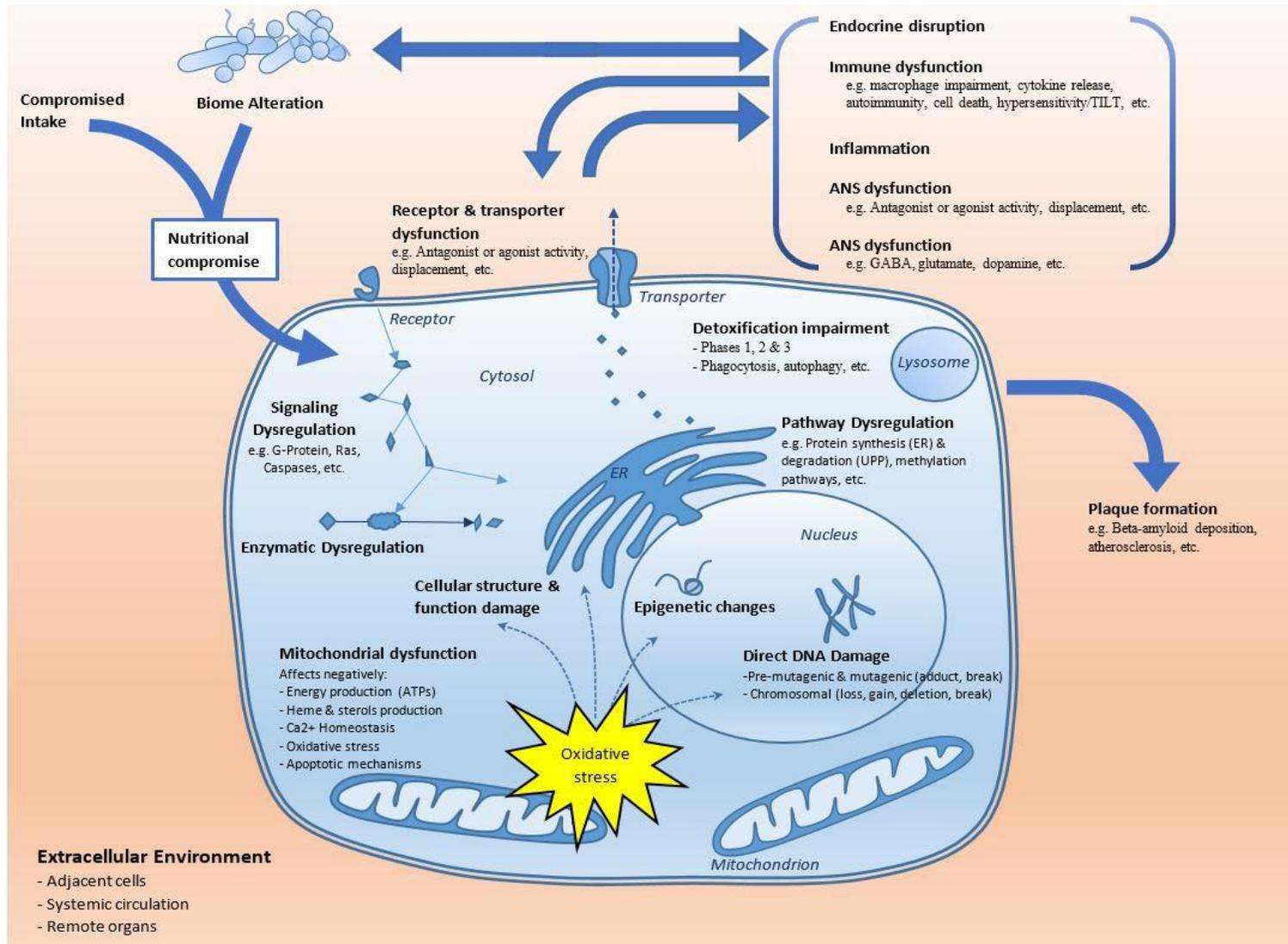


Figure 6 –Endocrine disruption and receptor dysregulation.

A simplified model of thyroid hormone feedback is used to illustrate the concept. Toxicants can have various disruptive effects and alter hormone synthesis, expression and reception. Phthalates have shown antagonist thyroid receptor activity while PCBs and PBDEs have shown both agonist and antagonist activity on thyroid receptors.

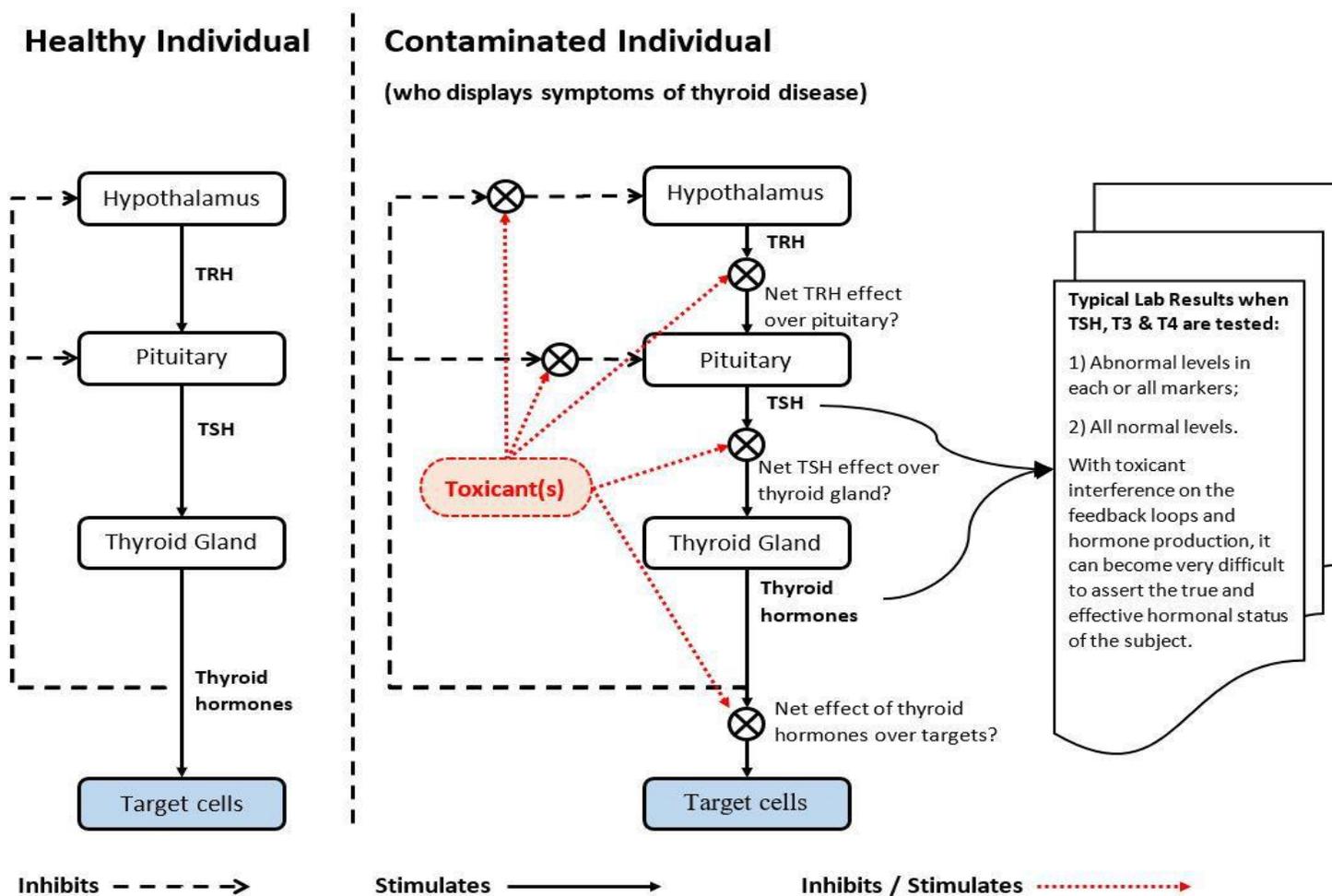
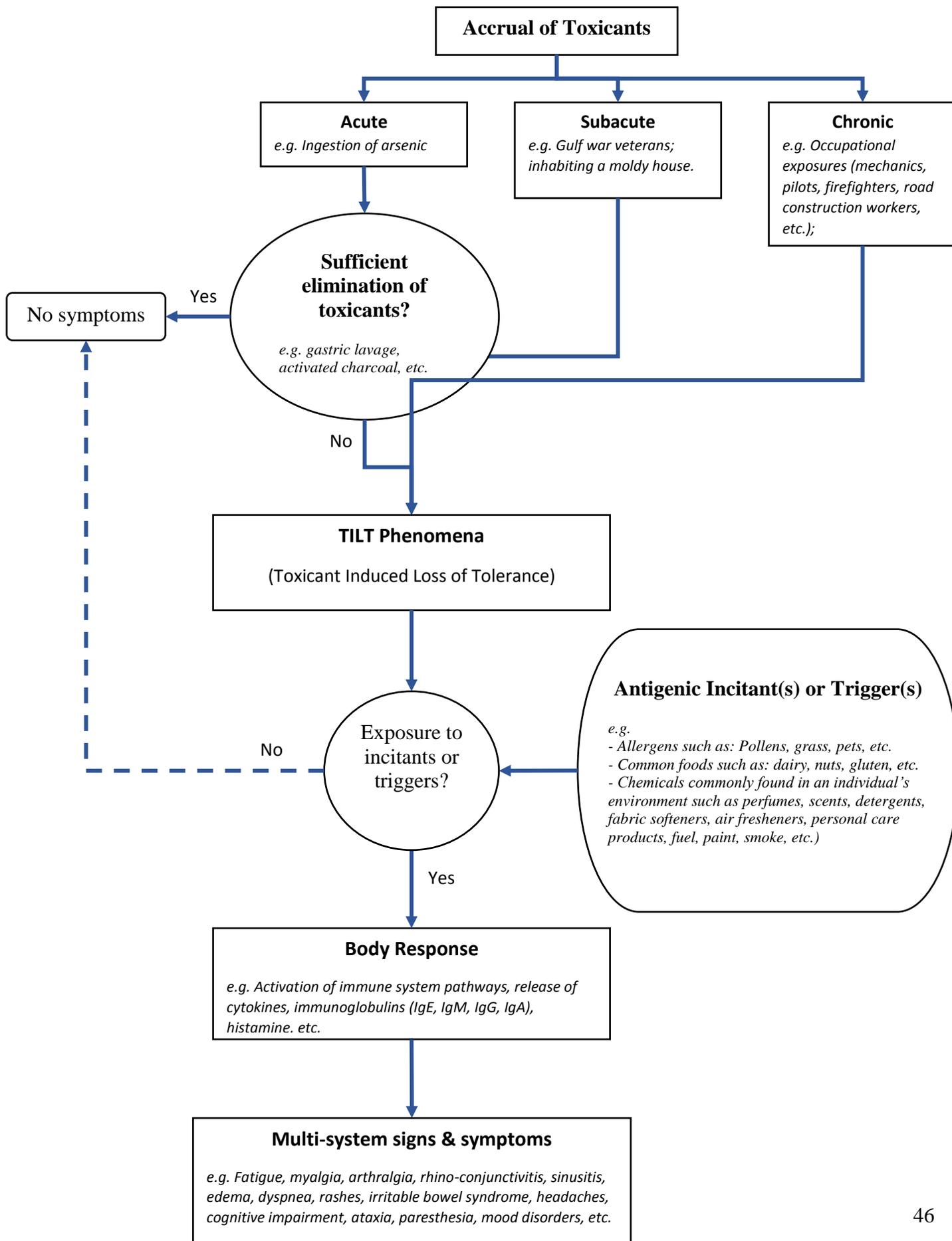


Figure 7 – Toxicant induced loss of tolerance (TILT) phenomena. As a result of toxicant bioaccumulation within the body, the immune system becomes oversensitive and responds to low dose levels of common environmental chemicals (e.g. perfume) or chemical structures (e.g. pollen) to which the same individual would have otherwise not reacted to previously.



References

1. NHANES – Fourth National Report on Exposure to Environmental Chemical Exposures, 2012. Available at <http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf> Accessed November 24, 2012.
2. Di Renzo GC, Conry JA, Blake J, DeFrancesco MS, DeNicola N, Martin JN, Jr., et al. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. *Int J Gynaecol Obstet.* 2015. doi: 10.1016/j.ijgo.2015.09.002. PubMed PMID: 26433469.
3. Centers for Disease Control and Prevention: Department of Health and Human Services. Fourth National Report on Human Exposure to Environmental Chemicals. Atlanta: Georgia. Updated Tables. Accessed April 14/2014 at [http://www.cdc.gov/exposurereport/pdf/FourthReport_UpdatedTables_Mar2013.pdf] 2013.
4. Health Canada. Canadian Health Measures Survey. Second report on human biomonitoring of environmental chemicals in Canada. Accessed on April 2, 2014 at [<http://www.hc-sc.gc.ca/ewh-semt/contaminants/human-humaine/chms-ecms-eng.php>]. 2013.
5. Jandacek RJ, Genuis SJ. An assessment of the intestinal lumen as a site for intervention in reducing body burdens of organochlorine compounds. *TheScientificWorldJournal.* 2013;2013:205621. Epub 2013/03/12. doi: 10.1155/2013/205621. PubMed PMID: 23476122; PubMed Central PMCID: PMC3582106.
6. Rat Genome Sequencing Project C. Genome sequence of the Brown Norway rat yields insights into mammalian evolution. *Nature.* 2004;428:493-521.
7. Welshons WV, Thayer KA, Judy BM, Taylor JA, Curran EM, vom Saal FS. Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. *Environ Health Perspect.* 2003;111(8):994-1006.
8. Canfield RL, Henderson CR, Jr., Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter. *N Engl J Med.* 2003;348(16):1517-26. PubMed PMID: 12700371.
9. Steenland K, Tinker S, Shankar A, Ducatman A. Association of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) with uric acid among adults with elevated community exposure to PFOA. *Environmental health perspectives.* 2010;118(2):229-33. Epub 2010/02/04. doi: 10.1289/ehp.0900940. PubMed PMID: 20123605; PubMed Central PMCID: PMC2831922.
10. Frisbee SJ, Shankar A, Knox SS, Steenland K, Savitz DA, Fletcher T, et al. Perfluorooctanoic acid, perfluorooctanesulfonate, and serum lipids in children and adolescents: results from the C8 Health Project. *Arch Pediatr Adolesc Med.* 2010;164(9):860-9. doi: 10.1001/archpediatrics.2010.163. PubMed PMID: 20819969; PubMed Central PMCID: PMC3116641.
11. Genuis S. Back to the future of healthcare: aetiology-centred medicine. *New Zealand Medical Journal.* 2005;118(1215):U1467.
12. Genuis SJ. What's out there making us sick? *J Environ Public Health.* 2012;605137.
13. Horton R. The neglected epidemic of chronic disease. *Lancet.* 2005;366:1514.
14. Perrin JM, Bloom SR, Gortmaker SL. The increase of childhood chronic conditions in the United States. *Jama.* 2007;297(24):2755-9. PubMed PMID: 17595277.
15. Genuis SJ. Our genes are not our destiny: incorporating molecular medicine into clinical practice. *J Eval Clin Pract.* 2008;14(1):94-102. PubMed PMID: 18211650.
16. Baker SM. Detoxification and healing: the key to optimal health. 1997.

17. Office of Genomics and Disease Prevention: Centers for Disease Control and Prevention. Department of Health and Human S. Gene-Environment Interaction Fact Sheet. 2000.
18. Rappaport SM, Smith MT. Epidemiology. Environment and disease risks. *Science*. 2010;330(6003):460-1. Epub 2010/10/23. doi: 10.1126/science.1192603. PubMed PMID: 20966241.
19. Wu S, Powers S, Zhu W, Hannun YA. Substantial contribution of extrinsic risk factors to cancer development. *Nature*. 2015. doi: 10.1038/nature16166. PubMed PMID: 26675728.
20. Selmi C, Leung PS, Sherr DH, Diaz M, Nyland JF, Monestier M, et al. Mechanisms of environmental influence on human autoimmunity: A national institute of environmental health sciences expert panel workshop. *J Autoimmun*. 2012. Epub 2012/07/04. doi: 10.1016/j.jaut.2012.05.007. PubMed PMID: 22749494.
21. Crone HD. Paracelsus: the man who defied medicine : his real contribution to medicine. Melbourne: Albarello Press. pp 1-183. . 2004.
22. Genuis SJ, Sears ME, Schwalfenberg G, Hope J, Bernhoft R. Clinical detoxification: elimination of persistent toxicants from the human body. *TheScientificWorldJournal*. 2013;2013:238347. Epub 2013/07/12. doi: 10.1155/2013/238347. PubMed PMID: 23844383; PubMed Central PMCID: PMC3691527.
23. Dijkers MP. The value of traditional reviews in the era of systematic reviewing. *Am J Phys Med Rehabil*. 2009;88(5):423-30. PubMed PMID: 19630127.
24. Crofton KM. Thyroid disrupting chemicals: mechanisms and mixtures. *Int J Androl*. 2008;31(2):209-23. doi: 10.1111/j.1365-2605.2007.00857.x. PubMed PMID: 18217984.
25. Brent GA. Environmental exposures and autoimmune thyroid disease. *Thyroid*. 2010;20(7):755-61. doi: 10.1089/thy.2010.1636. PubMed PMID: 20578899; PubMed Central PMCID: PMC2935336.
26. Cascio G, Schiera G, Di Liegro I. Dietary fatty acids in metabolic syndrome, diabetes and cardiovascular diseases. *Current diabetes reviews*. 2012;8(1):2-17. PubMed PMID: 22414056.
27. Pritchard JB. Toxic substances and cell membrane function. *Fed Proc*. 1979;38:2220-5.
28. Waseem M, Parvez S. Mitochondrial dysfunction mediated cisplatin induced toxicity: modulatory role of curcumin. *Food Chem Toxicol*. 2013;53:334-42. doi: 10.1016/j.fct.2012.11.055. PubMed PMID: 23246825.
29. Kumar R, Ansari KM, Chaudhari BP, Dhawan A, Dwivedi PD, Jain SK, et al. Topical application of ochratoxin A causes DNA damage and tumor initiation in mouse skin. *PLoS One*. 2012;7(10):e47280. doi: 10.1371/journal.pone.0047280. PubMed PMID: 23071775; PubMed Central PMCID: PMC3468467.
30. Chavan H, Krishnamurthy P. Polycyclic aromatic hydrocarbons (PAHs) mediate transcriptional activation of the ATP binding cassette transporter ABCB6 gene via the aryl hydrocarbon receptor (AhR). *J Biol Chem*. 2012;287(38):32054-68. doi: 10.1074/jbc.M112.371476. PubMed PMID: 22761424; PubMed Central PMCID: PMC3442536.
31. Langie SA, Koppen G, Desaulniers D, Al-Mulla F, Al-Temaimi R, Amedei A, et al. Causes of genome instability: the effect of low dose chemical exposures in modern society. *Carcinogenesis*. 2015;36 Suppl 1:S61-88. doi: 10.1093/carcin/bgv031. PubMed PMID: 26106144; PubMed Central PMCID: PMC4565613.
32. Van Houten B, Woshner V, Santos JH. Role of mitochondrial DNA in toxic responses to oxidative stress. *DNA Repair (Amst)*. 2006;5(2):145-52. doi: 10.1016/j.dnarep.2005.03.002. PubMed PMID: 15878696.
33. Al-Mousa F, Michelangeli F. Some commonly used brominated flame retardants cause Ca²⁺-ATPase inhibition, beta-amyloid peptide release and apoptosis in SH-SY5Y neuronal cells.

- PLoS One. 2012;7(4):e33059. Epub 2012/04/10. doi: 10.1371/journal.pone.0033059. PubMed PMID: 22485137; PubMed Central PMCID: PMC3317662.
34. O'Shaughnessy PJ, Monteiro A, Bhattacharya S, Fowler PA. Maternal smoking and fetal sex significantly affect metabolic enzyme expression in the human fetal liver. *J Clin Endocrinol Metab.* 2011;96(9):2851-60. doi: 10.1210/jc.2011-1437. PubMed PMID: 21715529.
 35. Grover P, Danadevi K, Mahboob M, Rozati R, Banu BS, Rahman MF. Evaluation of genetic damage in workers employed in pesticide production utilizing the Comet assay. *Mutagenesis.* 2003;18(2):201-5. PubMed PMID: 12621077.
 36. Garry VF, Schreinemachers D, Harkins ME, Griffith J. Pesticide applicators, biocides, and birth defects in rural Minnesota. *Environ Health Perspect.* 1996;104(4):394-9. PubMed PMID: 8732949; PubMed Central PMCID: PMC1469337.
 37. Lander BF, Knudsen LE, Gamborg MO, Jarventaus H, Norppa H. Chromosome aberrations in pesticide-exposed greenhouse workers. *Scandinavian journal of work, environment & health.* 2000;26(5):436-42. PubMed PMID: 11103843.
 38. Gomez-Arroyo S, Diaz-Sanchez Y, Meneses-Perez MA, Villalobos-Pietrini R, De Leon-Rodriguez J. Cytogenetic biomonitoring in a Mexican floriculture worker group exposed to pesticides. *Mutation research.* 2000;466(1):117-24. PubMed PMID: 10751733.
 39. Zeljezic D, Garaj-Vrhovac V. Sister chromatid exchange and proliferative rate index in the longitudinal risk assessment of occupational exposure to pesticides. *Chemosphere.* 2002;46(2):295-303. PubMed PMID: 11827288.
 40. Zhang Y, Sun LG, Ye LP, Wang B, Li Y. Lead-induced stress response in endoplasmic reticulum of astrocytes in CNS. *Toxicol Mech Methods.* 2008;18(9):751-7. doi: 10.1080/15376510802390908. PubMed PMID: 20020935.
 41. Yen YP, Tsai KS, Chen YW, Huang CF, Yang RS, Liu SH. Arsenic induces apoptosis in myoblasts through a reactive oxygen species-induced endoplasmic reticulum stress and mitochondrial dysfunction pathway. *Arch Toxicol.* 2012;86(6):923-33. doi: 10.1007/s00204-012-0864-9. PubMed PMID: 22622864.
 42. Kitamura M, Hiramatsu N. The oxidative stress: endoplasmic reticulum stress axis in cadmium toxicity. *Biometals.* 2010;23(5):941-50. doi: 10.1007/s10534-010-9296-2. PubMed PMID: 20130962.
 43. Chinta SJ, Rane A, Poksay KS, Bredesen DE, Andersen JK, Rao RV. Coupling endoplasmic reticulum stress to the cell death program in dopaminergic cells: effect of paraquat. *Neuromolecular Med.* 2008;10(4):333-42. doi: 10.1007/s12017-008-8047-9. PubMed PMID: 18773310; PubMed Central PMCID: PMC2818083.
 44. Hossain MM, Richardson JR. Mechanism of pyrethroid pesticide-induced apoptosis: role of calpain and the ER stress pathway. *Toxicol Sci.* 2011;122(2):512-25. doi: 10.1093/toxsci/kfr111. PubMed PMID: 21555338; PubMed Central PMCID: PMC3155085.
 45. Pesonen M, Pasanen M, Loikkanen J, Naukkarinen A, Hemmila M, Seulanto H, et al. Chloropicrin induces endoplasmic reticulum stress in human retinal pigment epithelial cells. *Toxicol Lett.* 2012;211(3):239-45. doi: 10.1016/j.toxlet.2012.04.002. PubMed PMID: 22516760.
 46. Mostafalou S, Abdollahi M. Pesticides and human chronic diseases: evidences, mechanisms, and perspectives. *Toxicol Appl Pharmacol.* 2013;268(2):157-77. doi: 10.1016/j.taap.2013.01.025. PubMed PMID: 23402800.
 47. Chen S, Melchior WB, Jr., Guo L. Endoplasmic reticulum stress in drug- and environmental toxicant-induced liver toxicity. *J Environ Sci Health C Environ Carcinog Ecotoxicol Rev.* 2014;32(1):83-104. doi: 10.1080/10590501.2014.881648. PubMed PMID: 24598041.

48. Rossignol DA, Frye RE. Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation in the brain of individuals with autism. *Front Physiol.* 2014;5:150. doi: 10.3389/fphys.2014.00150. PubMed PMID: 24795645; PubMed Central PMCID: PMC4001006.
49. Seyfried TN. Cancer as a mitochondrial metabolic disease. *Front Cell Dev Biol.* 2015;3:43. doi: 10.3389/fcell.2015.00043. PubMed PMID: 26217661; PubMed Central PMCID: PMC4493566.
50. Orrenius S, Nicotera P, Zhivotovsky B. Cell death mechanisms and their implications in toxicology. *Toxicological Sciences.* 2011;119(1):3-19.
51. Meyer JN, Leung MC, Rooney JP, Sandoel A, Hengartner MO, Kisby GE, et al. Mitochondria as a target of environmental toxicants. *Toxicol Sci.* 2013;134(1):1-17. doi: 10.1093/toxsci/kft102. PubMed PMID: 23629515; PubMed Central PMCID: PMC3693132.
52. Pearson JN, Patel M. The role of oxidative stress in organophosphate and nerve agent toxicity. *Ann N Y Acad Sci.* 2016. doi: 10.1111/nyas.13115. PubMed PMID: 27371936.
53. Habertzell P, O'Toole TE, Bhatnagar A, Conklin DJ. Exposure to Fine Particulate Air Pollution Causes Vascular Insulin Resistance by Inducing Pulmonary Oxidative Stress. *Environ Health Perspect.* 2016. doi: 10.1289/EHP212. PubMed PMID: 27128347.
54. Klaunig JE, Kamendulis LM. The role of oxidative stress in carcinogenesis. *Annu Rev Pharmacol Toxicol.* 2004;44:239-67. doi: 10.1146/annurev.pharmtox.44.101802.121851. PubMed PMID: 14744246.
55. Sakac V, Sakac M. Free oxygen radicals and kidney diseases--part I. *Med Pregl.* 2000;53(9-10):463-74. PubMed PMID: 11320727.
56. Jomova K, Vondrakova D, Lawson M, Valko M. Metals, oxidative stress and neurodegenerative disorders. *Mol Cell Biochem.* 2010;345(1-2):91-104. Epub 2010/08/24. doi: 10.1007/s11010-010-0563-x. PubMed PMID: 20730621.
57. Valko M, Rhodes CJ, Moncol J, Izakovic M, Mazur M. Free radicals, metals and antioxidants in oxidative stress-induced cancer. *Chem Biol Interact.* 2006;160(1):1-40. doi: 10.1016/j.cbi.2005.12.009. PubMed PMID: 16430879.
58. James SJ, Cutler P, Melnyk S, Jernigan S, Janak L, Gaylor DW, et al. Metabolic biomarkers of increased oxidative stress and impaired methylation capacity in children with autism. *Am J Clin Nutr.* 2004;80(6):1611-7. PubMed PMID: 15585776.
59. Joseph N, Zhang-James Y, Perl A, Faraone SV. Oxidative Stress and ADHD: A Meta-Analysis. *J Atten Disord.* 2015;19(11):915-24. doi: 10.1177/1087054713510354. PubMed PMID: 24232168.
60. Hwang O. Role of oxidative stress in Parkinson's disease. *Exp Neurobiol.* 2013;22(1):11-7. doi: 10.5607/en.2013.22.1.11. PubMed PMID: 23585717; PubMed Central PMCID: PMC3620453.
61. Valko M, Leibfritz D, Moncol J, Cronin MT, Mazur M, Telser J. Free radicals and antioxidants in normal physiological functions and human disease. *Int J Biochem Cell Biol.* 2007;39(1):44-84. doi: 10.1016/j.biocel.2006.07.001. PubMed PMID: 16978905.
62. Pohanka M. Alzheimer's disease and oxidative stress: a review. *Curr Med Chem.* 2014;21(3):356-64. PubMed PMID: 24059239.
63. Bonomini F, Tengattini S, Fabiano A, Bianchi R, Rezzani R. Atherosclerosis and oxidative stress. *Histol Histopathol.* 2008;23(3):381-90. PubMed PMID: 18072094.
64. Singh N, Dhalla AK, Seneviratne C, Singal PK. Oxidative stress and heart failure. *Mol Cell Biochem.* 1995;147(1-2):77-81. PubMed PMID: 7494558.
65. Ramond A, Godin-Ribuot D, Ribouot C, Totoston P, Koritchneva I, Cachot S, et al. Oxidative stress mediates cardiac infarction aggravation induced by intermittent hypoxia. *Fundam*

- Clin Pharmacol. 2013;27(3):252-61. doi: 10.1111/j.1472-8206.2011.01015.x. PubMed PMID: 22145601.
66. Arican O, Kurutas EB. Oxidative stress in the blood of patients with active localized vitiligo. *Acta Dermatovenerol Alp Pannonica Adriat.* 2008;17(1):12-6. PubMed PMID: 18454264.
 67. Kennedy G, Spence VA, McLaren M, Hill A, Underwood C, Belch JJ. Oxidative stress levels are raised in chronic fatigue syndrome and are associated with clinical symptoms. *Free Radic Biol Med.* 2005;39(5):584-9. doi: 10.1016/j.freeradbiomed.2005.04.020. PubMed PMID: 16085177.
 68. Upham BL, Wagner JG. Toxicant-induced oxidative stress in cancer. *Toxicol Sci.* 2001;64(1):1-3. PubMed PMID: 11606793.
 69. Valko M, Morris H, Cronin MT. Metals, toxicity and oxidative stress. *Current medicinal chemistry.* 2005;12(10):1161-208. Epub 2005/05/17. PubMed PMID: 15892631.
 70. Jomova K, Valko M. Advances in metal-induced oxidative stress and human disease. *Toxicology.* 2011;283(2-3):65-87. doi: 10.1016/j.tox.2011.03.001. PubMed PMID: 21414382.
 71. Sahnoun Z, Jamoussi K, Zeghal KM. Free radicals and antioxidants: human physiology, pathology and therapeutic aspects. *Therapie.* 1997;52(4):251-70. PubMed PMID: 9437876.
 72. Cui Y, Chen X, Zhou Z, Lei Y, Ma M, Cao R, et al. Prenatal exposure to nanoparticulate titanium dioxide enhances depressive-like behaviors in adult rats. *Chemosphere.* 2014;96:99-104. doi: 10.1016/j.chemosphere.2013.07.051. PubMed PMID: 23972732.
 73. Liu BH, Wu TS, Yu FY, Su CC. Induction of oxidative stress response by the mycotoxin patulin in mammalian cells. *Toxicol Sci.* 2007;95(2):340-7. doi: 10.1093/toxsci/kfl156. PubMed PMID: 17090621.
 74. Doi K, Uetsuka K. Mechanisms of mycotoxin-induced neurotoxicity through oxidative stress-associated pathways. *Int J Mol Sci.* 2011;12(8):5213-37. doi: 10.3390/ijms12085213. PubMed PMID: 21954354; PubMed Central PMCID: PMC3179161.
 75. Victorino VJ, Pizzatti L, Michelletti P, Panis C. Oxidative stress, redox signaling and cancer chemoresistance: putting together the pieces of the puzzle. *Curr Med Chem.* 2014;21(28):3211-26. PubMed PMID: 24934351.
 76. Gu X, Manautou JE. Molecular mechanisms underlying chemical liver injury. *Expert Rev Mol Med.* 2012;14:e4. doi: 10.1017/S1462399411002110. PubMed PMID: 22306029; PubMed Central PMCID: PMC3704158.
 77. Lippmann M, (ed). *Environmental Toxicants: Human Exposures and Their Health Effects.* Third Edition. Hoboken, New Jersey: John Wiley & Sons. 2009.
 78. Roberts RA, Smith RA, Safe S, Szabo C, Tjalkens RB, Robertson FM. Toxicological and pathophysiological roles of reactive oxygen and nitrogen species. *Toxicology.* 2010;276(2):85-94. doi: 10.1016/j.tox.2010.07.009. PubMed PMID: 20643181.
 79. Sorrenti V, Di Giacomo C, Acquaviva R, Barbagallo I, Bognanno M, Galvano F. Toxicity of ochratoxin a and its modulation by antioxidants: a review. *Toxins (Basel).* 2013;5(10):1742-66. doi: 10.3390/toxins5101742. PubMed PMID: 24152986; PubMed Central PMCID: PMC3813909.
 80. O'Neill HC, Orlicky DJ, Hendry-Hofer TB, Loader JE, Day BJ, White CW. Role of reactive oxygen and nitrogen species in olfactory epithelial injury by the sulfur mustard analogue 2-chloroethyl ethyl sulfide. *Am J Respir Cell Mol Biol.* 2011;45(2):323-31. doi: 10.1165/rcmb.2010-0214OC. PubMed PMID: 21642592; PubMed Central PMCID: PMC3175559.
 81. Pacher P, Beckman JS, Liaudet L. Nitric oxide and peroxynitrite in health and disease. *Physiol Rev.* 2007;87(1):315-424. doi: 10.1152/physrev.00029.2006. PubMed PMID: 17237348; PubMed Central PMCID: PMC2248324.

82. Calcerrada P, Peluffo G, Radi R. Nitric oxide-derived oxidants with a focus on peroxynitrite: molecular targets, cellular responses and therapeutic implications. *Curr Pharm Des.* 2011;17(35):3905-32. PubMed PMID: 21933142.
83. Islam BU, Habib S, Ahmad P, Allarakha S, Moinuddin, Ali A. Pathophysiological Role of Peroxynitrite Induced DNA Damage in Human Diseases: A Special Focus on Poly(ADP-ribose) Polymerase (PARP). *Indian J Clin Biochem.* 2015;30(4):368-85. doi: 10.1007/s12291-014-0475-8. PubMed PMID: 26788021; PubMed Central PMCID: PMC4712174.
84. Hooper DC, Scott GS, Zborek A, Mikheeva T, Kean RB, Koprowski H, et al. Uric acid, a peroxynitrite scavenger, inhibits CNS inflammation, blood-CNS barrier permeability changes, and tissue damage in a mouse model of multiple sclerosis. *FASEB J.* 2000;14(5):691-8. PubMed PMID: 10744626.
85. Ichihara M, Sobue S, Ito M, Ito M, Hirayama M, Ohno K. Beneficial biological effects and the underlying mechanisms of molecular hydrogen - comprehensive review of 321 original articles. *Med Gas Res.* 2015;5:12. doi: 10.1186/s13618-015-0035-1. PubMed PMID: 26483953; PubMed Central PMCID: PMC4610055.
86. Ohta S. Molecular hydrogen as a preventive and therapeutic medical gas: initiation, development and potential of hydrogen medicine. *Pharmacol Ther.* 2014;144(1):1-11. doi: 10.1016/j.pharmthera.2014.04.006. PubMed PMID: 24769081.
87. Vuong AM, Webster GM, Romano ME, Braun JM, Zoeller RT, Hoofnagle AN, et al. Maternal Polybrominated Diphenyl Ether (PBDE) Exposure and Thyroid Hormones in Maternal and Cord Sera: The HOME Study, Cincinnati, USA. *Environ Health Perspect.* 2015;123(10):1079-85. doi: 10.1289/ehp.1408996. PubMed PMID: 25893858; PubMed Central PMCID: PMC4590759.
88. Shen O, Du G, Sun H, Wu W, Jiang Y, Song L, et al. Comparison of in vitro hormone activities of selected phthalates using reporter gene assays. *Toxicol Lett.* 2009;191(1):9-14. doi: 10.1016/j.toxlet.2009.07.019. PubMed PMID: 19643168.
89. Stavenes Andersen I, Voie OA, Fonnum F, Mariussen E. Effects of methyl mercury in combination with polychlorinated biphenyls and brominated flame retardants on the uptake of glutamate in rat brain synaptosomes: a mathematical approach for the study of mixtures. *Toxicol Sci.* 2009;112(1):175-84. doi: 10.1093/toxsci/kfp178. PubMed PMID: 19700605.
90. Mariussen E, Fonnum F. The effect of brominated flame retardants on neurotransmitter uptake into rat brain synaptosomes and vesicles. *Neurochem Int.* 2003;43(4-5):533-42. PubMed PMID: 12742101.
91. Hou L, Zhang X, Wang D, Baccarelli A. Environmental chemical exposures and human epigenetics. *International journal of epidemiology.* 2012;41(1):79-105. Epub 2012/01/19. doi: 10.1093/ije/dyr154. PubMed PMID: 22253299; PubMed Central PMCID: PMC3304523.
92. Relton CL, Davey Smith G. Epigenetic epidemiology of common complex disease: prospects for prediction, prevention, and treatment. *PLoS medicine.* 2010;7(10):e1000356. doi: 10.1371/journal.pmed.1000356. PubMed PMID: 21048988; PubMed Central PMCID: PMC2964338.
93. Anway MD, Skinner MK. Epigenetic programming of the germ line: effects of endocrine disruptors on the development of transgenerational disease. *Reprod Biomed Online.* 2008;16(1):23-5. Epub 2008/02/07. PubMed PMID: 18252044.
94. Skinner MK. Role of epigenetics in developmental biology and transgenerational inheritance. *Birth Defects Res C Embryo Today.* 2011;93(1):51-5. Epub 2011/03/23. doi: 10.1002/bdrc.20199. PubMed PMID: 21425441.
95. McClure EA, North CM, Kaminski NE, Goodman JI. Changes in DNA methylation and gene expression during 2,3,7,8-tetrachlorodibenzo-p-dioxin-induced suppression of the

- lipopolysaccharide-stimulated IgM response in splenocytes. *Toxicol Sci.* 2011;120(2):339-48. doi: 10.1093/toxsci/kfq396. PubMed PMID: 21212295; PubMed Central PMCID: PMC3061478.
96. Dammann RH, Kirsch S, Schagdarsurengin U, Dansranjav T, Gradhand E, Schmitt WD, et al. Frequent aberrant methylation of the imprinted IGF2/H19 locus and LINE1 hypomethylation in ovarian carcinoma. *Int J Oncol.* 2010;36(1):171-9. PubMed PMID: 19956846.
97. Bitto A, Pizzino G, Irrera N, Galfo F, Squadrito F. Epigenetic modifications due to heavy metals exposure in children living in polluted areas. *Curr Genomics.* 2014;15(6):464-8. doi: 10.2174/138920291506150106153336. PubMed PMID: 25646074; PubMed Central PMCID: PMC4311390.
98. Gravina S, Vijg J. Epigenetic factors in aging and longevity. *Pflugers Arch.* 2010;459(2):247-58. doi: 10.1007/s00424-009-0730-7. PubMed PMID: 19768466.
99. Mizuno N, Niwa T, Yotsumoto Y, Sugiyama Y. Impact of drug transporter studies on drug discovery and development. *Pharmacol Rev.* 2003;55(3):425-61. doi: 10.1124/pr.55.3.1. PubMed PMID: 12869659.
100. Jakoby WB, Ziegler DM. The enzymes of detoxication. *J Biol Chem.* 1990;265(34):20715-8. PubMed PMID: 2249981.
101. Zmrzljak UP, Rozman D. Circadian regulation of the hepatic endobiotic and xenobiotic detoxification pathways: the time matters. *Chem Res Toxicol.* 2012;25(4):811-24. doi: 10.1021/tx200538r. PubMed PMID: 22303888.
102. Omiecinski CJ, Vanden Heuvel JP, Perdew GH, Peters JM. Xenobiotic metabolism, disposition, and regulation by receptors: from biochemical phenomenon to predictors of major toxicities. *Toxicol Sci.* 2011;120 Suppl 1:S49-75. doi: 10.1093/toxsci/kfq338. PubMed PMID: 21059794; PubMed Central PMCID: PMC3145385.
103. Schlichting I, Berendzen J, Chu K, Stock AM, Maves SA, Benson DE, et al. The catalytic pathway of cytochrome p450cam at atomic resolution. *Science.* 2000;287(5458):1615-22. PubMed PMID: 10698731.
104. Gilbert KM, Pumford NR, Blossom SJ. Environmental Contaminant Trichloroethylene Promotes Autoimmune Disease and Inhibits T-cell Apoptosis in MRL(+/-) Mice. *Journal of immunotoxicology.* 2006;3(4):263-7. PubMed PMID: 18958707.
105. Guengerich FP. Common and uncommon cytochrome P450 reactions related to metabolism and chemical toxicity. *Chem Res Toxicol.* 2001;14(6):611-50. PubMed PMID: 11409933.
106. Liston HL, Markowitz JS, DeVane CL. Drug glucuronidation in clinical psychopharmacology. *J Clin Psychopharmacol.* 2001;21(5):500-15. PubMed PMID: 11593076.
107. Johnson CH, Patterson AD, Idle JR, Gonzalez FJ. Xenobiotic metabolomics: major impact on the metabolome. *Annu Rev Pharmacol Toxicol.* 2012;52:37-56. doi: 10.1146/annurev-pharmtox-010611-134748. PubMed PMID: 21819238.
108. Strolin Benedetti M. FAD-dependent enzymes involved in the metabolic oxidation of xenobiotics. *Ann Pharm Fr.* 2011;69(1):45-52. doi: 10.1016/j.pharma.2010.10.004. PubMed PMID: 21296217.
109. Homolya L, Varadi A, Sarkadi B. Multidrug resistance-associated proteins: Export pumps for conjugates with glutathione, glucuronate or sulfate. *Biofactors.* 2003;17(1-4):103-14. PubMed PMID: 12897433.
110. Commandeur JN, Stijntjes GJ, Vermeulen NP. Enzymes and transport systems involved in the formation and disposition of glutathione S-conjugates. Role in bioactivation and detoxication mechanisms of xenobiotics. *Pharmacol Rev.* 1995;47(2):271-330. PubMed PMID: 7568330.
111. Nicklisch SC, Rees SD, McGrath AP, Gokirmak T, Bonito LT, Vermeer LM, et al. Global marine pollutants inhibit P-glycoprotein: Environmental levels, inhibitory effects, and cocrystal

- structure. *Sci Adv.* 2016;2(4):e1600001. doi: 10.1126/sciadv.1600001. PubMed PMID: 27152359; PubMed Central PMCID: PMC4846432.
112. Samsel A, S S. Glyphosate's Suppression of Cytochrome P450 Enzymes and Amino Acid Biosynthesis by the Gut Microbiome: Pathways to Modern Diseases *Entropy* 2013;15(4):1416-63.
113. Katsnelson BA, Minigaliyeva IA, Degtyareva TD, Privalova LI, Beresneva TA. Does a concomitant exposure to lead influence unfavorably the naphthalene subchronic toxicity and toxicokinetics? *Environ Toxicol Chem.* 2014;33(1):152-7. doi: 10.1002/etc.2405. PubMed PMID: 24114755.
114. Varaksin AN, Katsnelson BA, Panov VG, Privalova LI, Kireyeva EP, Valamina IE, et al. Some considerations concerning the theory of combined toxicity: a case study of subchronic experimental intoxication with cadmium and lead. *Food Chem Toxicol.* 2014;64:144-56. doi: 10.1016/j.fct.2013.11.024. PubMed PMID: 24291454.
115. Giordano G, Kavanagh TJ, Costa LG. Neurotoxicity of a polybrominated diphenyl ether mixture (DE-71) in mouse neurons and astrocytes is modulated by intracellular glutathione levels. *Toxicol Appl Pharmacol.* 2008;232(2):161-8. doi: 10.1016/j.taap.2008.06.018. PubMed PMID: 18656495; PubMed Central PMCID: PMC2634604.
116. Stefanis L. alpha-Synuclein in Parkinson's disease. *Cold Spring Harb Perspect Med.* 2012;2(2):a009399. doi: 10.1101/cshperspect.a009399. PubMed PMID: 22355802; PubMed Central PMCID: PMC3281589.
117. Chin-Chan M, Navarro-Yepes J, Quintanilla-Vega B. Environmental pollutants as risk factors for neurodegenerative disorders: Alzheimer and Parkinson diseases. *Front Cell Neurosci.* 2015;9:124. doi: 10.3389/fncel.2015.00124. PubMed PMID: 25914621; PubMed Central PMCID: PMC4392704.
118. Dardiotis E, Xiomerisiou G, Hadjichristodoulou C, Tsatsakis AM, Wilks MF, Hadjigeorgiou GM. The interplay between environmental and genetic factors in Parkinson's disease susceptibility: the evidence for pesticides. *Toxicology.* 2013;307:17-23. doi: 10.1016/j.tox.2012.12.016. PubMed PMID: 23295711.
119. Naughton C, O'Toole D, Kirik D, Dowd E. Interaction between subclinical doses of the Parkinson's disease associated gene, α -synuclein, and the pesticide, rotenone, precipitates motor dysfunction and nigrostriatal neurodegeneration in rats. *Behav Brain Res* 2017;316:160-8.
120. Navarro-Yepes J, Anandhan A, Bradley E, Bohovych I, Yarabe B, de Jong A, et al. Inhibition of Protein Ubiquitination by Paraquat and 1-Methyl-4-Phenylpyridinium Impairs Ubiquitin-Dependent Protein Degradation Pathways. *Mol Neurobiol.* 2016;53(8):5229-51. doi: 10.1007/s12035-015-9414-9. PubMed PMID: 26409479; PubMed Central PMCID: PMC4842169.
121. Jadiya P, Nazir A. Environmental toxicants as extrinsic epigenetic factors for parkinsonism: studies employing transgenic *C. elegans* model. *CNS Neurol Disord Drug Targets.* 2012;11(8):976-83. PubMed PMID: 23244436.
122. Yegambaram M, Manivannan B, Beach TG, Halden RU. Role of environmental contaminants in the etiology of Alzheimer's disease: a review. *Curr Alzheimer Res.* 2015;12(2):116-46. PubMed PMID: 25654508; PubMed Central PMCID: PMC4428475.
123. Al-Mousa F, Michelangeli F. The sarcoplasmic-endoplasmic reticulum Ca(2+)-ATPase (SERCA) is the likely molecular target for the acute toxicity of the brominated flame retardant hexabromocyclododecane (HBCD). *Chem Biol Interact.* 2014;207:1-6.
124. Hakk H, Letcher RJ. Metabolism in the toxicokinetics and fate of brominated flame retardants--a review. *Environ Int.* 2003;29(6):801-28. doi: 10.1016/S0160-4120(03)00109-0. PubMed PMID: 12850098.

125. Ramos KS, Bowes RC, 3rd, Ou X, Weber TJ. Responses of vascular smooth muscle cells to toxic insult: cellular and molecular perspectives for environmental toxicants. *J Toxicol Environ Health*. 1994;43(4):419-40. doi: 10.1080/15287399409531932. PubMed PMID: 7990168.
126. Omaye ST. Metabolic modulation of carbon monoxide toxicity. *Toxicology*. 2002;180(2):139-50. PubMed PMID: 12324190.
127. Pittman RN. Regulation of Tissue Oxygenation, Chapter 4, Oxygen Transport, San Rafael (CA): Morgan & Claypool Life Sciences; 2011.
128. Kim HS, Kim YJ, Seo YR. An Overview of Carcinogenic Heavy Metal: Molecular Toxicity Mechanism and Prevention. *J Cancer Prev*. 2015;20(4):232-40. doi: 10.15430/JCP.2015.20.4.232. PubMed PMID: 26734585; PubMed Central PMCID: PMC4699750.
129. Kass GE, Nicotera P, Orrenius S. Effects of xenobiotics on signal transduction and Ca²⁺-mediated processes in mammalian cells. *Princess Takamatsu Symp*. 1990;21:213-26. PubMed PMID: 1966887.
130. Li Z, Dong T, Proschel C, Noble M. Chemically diverse toxicants converge on Fyn and c-Cbl to disrupt precursor cell function. *PLoS Biol*. 2007;5(2):e35. doi: 10.1371/journal.pbio.0050035. PubMed PMID: 17298174; PubMed Central PMCID: PMC1790953.
131. Tramutola A, Di Domenico F, Barone E, Perluigi M, Butterfield DA. It Is All about (U)biqutin: Role of Altered Ubiquitin-Proteasome System and UCHL1 in Alzheimer Disease. *Oxid Med Cell Longev*. 2016;2016:2756068. doi: 10.1155/2016/2756068. PubMed PMID: 26881020; PubMed Central PMCID: PMC4736377.
132. Salome M, Campos J, Keeshan K. TRIB2 and the ubiquitin proteasome system in cancer. *Biochemical Society transactions*. 2015;43(5):1089-94. doi: 10.1042/BST20150103. PubMed PMID: 26517929.
133. Yu X, Robinson JF, Sidhu JS, Hong S, Faustman EM. A system-based comparison of gene expression reveals alterations in oxidative stress, disruption of ubiquitin-proteasome system and altered cell cycle regulation after exposure to cadmium and methylmercury in mouse embryonic fibroblast. *Toxicol Sci*. 2010;114(2):356-77. doi: 10.1093/toxsci/kfq003. PubMed PMID: 20061341; PubMed Central PMCID: PMC2840217.
134. Rhodes SL, Fitzmaurice AG, Cockburn M, Bronstein JM, Sinsheimer JS, Ritz B. Pesticides that inhibit the ubiquitin-proteasome system: effect measure modification by genetic variation in SKP1 in Parkinsons disease. *Environ Res*. 2013;126:1-8. doi: 10.1016/j.envres.2013.08.001. PubMed PMID: 23988235; PubMed Central PMCID: PMC3832349.
135. Orrenius S, Kaminsky VO, Zhivotovsky B. Autophagy in toxicology: cause or consequence? *Annu Rev Pharmacol Toxicol*. 2013;53:275-97. doi: 10.1146/annurev-pharmtox-011112-140210. PubMed PMID: 23072380.
136. Dagda RK, Das Banerjee T, Janda E. How Parkinsonian toxins dysregulate the autophagy machinery. *Int J Mol Sci*. 2013;14(11):22163-89. doi: 10.3390/ijms141122163. PubMed PMID: 24217228; PubMed Central PMCID: PMC3856058.
137. Wu F, Xu HD, Guan JJ, Hou YS, Gu JH, Zhen XC, et al. Rotenone impairs autophagic flux and lysosomal functions in Parkinson's disease. *Neuroscience*. 2015;284:900-11. doi: 10.1016/j.neuroscience.2014.11.004. PubMed PMID: 25446361.
138. Song XY, Li JN, Wu YP, Zhang B, Li BX. Atrazine Causes Autophagy- and Apoptosis-Related Neurodegenerative Effects in Dopaminergic Neurons in the Rat Nigrostriatal Dopaminergic System. *Int J Mol Sci*. 2015;16(6):13490-506. doi: 10.3390/ijms160613490. PubMed PMID: 26075868; PubMed Central PMCID: PMC4490505.

139. Kabir ER, Rahman MS, Rahman I. A review on endocrine disruptors and their possible impacts on human health. *Environ Toxicol Pharmacol*. 2015;40(1):241-58. doi: 10.1016/j.etap.2015.06.009. PubMed PMID: 26164742.
140. Maqbool F, Mostafalou S, Bahadar H, Abdollahi M. Review of endocrine disorders associated with environmental toxicants and possible involved mechanisms. *Life sciences*. 2016;145:265-73. doi: 10.1016/j.lfs.2015.10.022. PubMed PMID: 26497928.
141. The Prague Declaration on Endocrine Disruption -126 Signatories. Meeting for international group of scientists convened in Prague. May 1-12, 2005.
142. Mnif W, Hassine AI, Bouaziz A, Bartegi A, Thomas O, Roig B. Effect of endocrine disruptor pesticides: a review. *Int J Environ Res Public Health*. 2011;8(6):2265-303. doi: 10.3390/ijerph8062265. PubMed PMID: 21776230; PubMed Central PMCID: PMC3138025.
143. Hendriks HS, Antunes Fernandes EC, Bergman A, van den Berg M, Westerink RH. PCB-47, PBDE-47, and 6-OH-PBDE-47 differentially modulate human GABAA and alpha4beta2 nicotinic acetylcholine receptors. *Toxicological Sciences*. 2010;118(2):635-42.
144. World Health Organization. United Nations Environment Program: State of the science of endocrine disrupting chemicals. Accessed 20 Feb 2013 at [<http://www.who.int/ceh/publications/endocrine/en/index.html>]. 2012.
145. Guerrero-Bosagna C, Skinner MK. Environmentally induced epigenetic transgenerational inheritance of phenotype and disease. *Molecular and cellular endocrinology*. 2012;354(1-2):3-8. Epub 2011/10/25. doi: 10.1016/j.mce.2011.10.004. PubMed PMID: 22020198; PubMed Central PMCID: PMC3312615.
146. Guerrero-Bosagna CM, Skinner MK. Environmental epigenetics and phytoestrogen/phytochemical exposures. *The Journal of steroid biochemistry and molecular biology*. 2012. Epub 2013/01/01. doi: 10.1016/j.jsbmb.2012.12.011. PubMed PMID: 23274117.
147. Skinner MK, Manikkam M, Guerrero-Bosagna C. Epigenetic transgenerational actions of endocrine disruptors. *Reproductive toxicology*. 2011;31(3):337-43. Epub 2010/11/09. doi: 10.1016/j.reprotox.2010.10.012. PubMed PMID: 21055462; PubMed Central PMCID: PMC3068236.
148. Takser L, Mergler D, Baldwin M, de Grosbois S, Smargiassi A, Lafond J. Thyroid hormones in pregnancy in relation to environmental exposure to organochlorine compounds and mercury. *Environ Health Perspect*. 2005;113(8):1039-45. PubMed PMID: 16079076; PubMed Central PMCID: PMC1280346.
149. Jensen AA, Leffers H. Emerging endocrine disruptors: perfluoroalkylated substances. *Int J Androl*. 2008;31(2):161-9. doi: 10.1111/j.1365-2605.2008.00870.x. PubMed PMID: 18315716.
150. Rubin BS. Bisphenol A: an endocrine disruptor with widespread exposure and multiple effects. *J Steroid Biochem Mol Biol*. 2011;127(1-2):27-34. doi: 10.1016/j.jsbmb.2011.05.002. PubMed PMID: 21605673.
151. Colon I, Caro D, Bourdony CJ, Rosario O. Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. *Environ Health Perspect*. 2000;108(9):895-900.
152. Aguilar-Garduno C, Lacasana M, Blanco-Munoz J, Rodriguez-Barranco M, Hernandez AF, Bassol S, et al. Changes in male hormone profile after occupational organophosphate exposure. A longitudinal study. *Toxicology*. 2013;307:55-65. Epub 2012/11/17. doi: 10.1016/j.tox.2012.11.001. PubMed PMID: 23153546.
153. Gray LE, Jr., Wolf C, Lambright C, Mann P, Price M, Cooper RL, et al. Administration of potentially antiandrogenic pesticides (procymidone, linuron, iprodione, chlozolinate, p,p'-DDE, and ketoconazole) and toxic substances (dibutyl- and diethylhexyl phthalate, PCB 169, and ethane dimethane sulphonate) during sexual differentiation produces diverse profiles of reproductive

- malformations in the male rat. *Toxicology and industrial health*. 1999;15(1-2):94-118. Epub 1999/04/03. PubMed PMID: 10188194.
154. Birnbaum LS. Endocrine effects of prenatal exposure to PCBs, dioxins, and other xenobiotics: implications for policy and future research. *Environ Health Perspect*. 1994;102(8):676-9.
155. Final amended report on the safety assessment of Methylparaben, Ethylparaben, Propylparaben, Isopropylparaben, Butylparaben, Isobutylparaben, and Benzylparaben as used in cosmetic products. *Int J Toxicol*. 2008;27 Suppl 4:1-82. Epub 2009/01/06. doi: 10.1080/10915810802548359. PubMed PMID: 19101832.
156. Camacho L, Latendresse JR, Muskhelishvili L, Patton R, Bowyer JF, Thomas M, et al. Effects of acrylamide exposure on serum hormones, gene expression, cell proliferation, and histopathology in male reproductive tissues of Fischer 344 rats. *Toxicology letters*. 2012;211(2):135-43. Epub 2012/03/31. doi: 10.1016/j.toxlet.2012.03.007. PubMed PMID: 22459607.
157. Frizzell C, Ndossi D, Kalayou S, Eriksen GS, Verhaegen S, Sorlie M, et al. An in vitro investigation of endocrine disrupting effects of the mycotoxin alternariol. *Toxicol Appl Pharmacol*. 2013;271(1):64-71. doi: 10.1016/j.taap.2013.05.002. PubMed PMID: 23665424.
158. Frizzell C, Verhaegen S, Ropstad E, Elliott CT, Connolly L. Endocrine disrupting effects of ochratoxin A at the level of nuclear receptor activation and steroidogenesis. *Toxicol Lett*. 2013;217(3):243-50. doi: 10.1016/j.toxlet.2012.12.018. PubMed PMID: 23296098.
159. Takiguchi M, Yoshihara S. New aspects of cadmium as endocrine disruptor. *Environ Sci*. 2006;13(2):107-16. PubMed PMID: 16788562.
160. Kortenkamp A. Are cadmium and other heavy metal compounds acting as endocrine disrupters? *Met Ions Life Sci*. 2011;8:305-17. PubMed PMID: 21473385.
161. Balthazart J. Minireview: Hormones and human sexual orientation. *Endocrinology*. 2011;152(8):2937-47. doi: 10.1210/en.2011-0277. PubMed PMID: 21693676; PubMed Central PMCID: PMC3138231.
162. Hood E. Are EDCs blurring issues of gender? *Environ Health Perspect*. 2005;113(10):A670-7. PubMed PMID: 16203228; PubMed Central PMCID: PMC1281309.
163. Chevrier J, Harley KG, Bradman A, Gharbi M, Sjodin A, Eskenazi B. Polybrominated diphenyl ether (PBDE) flame retardants and thyroid hormone during pregnancy. *Environ Health Perspect*. 2010;118(10):1444-9. doi: 10.1289/ehp.1001905. PubMed PMID: 20562054; PubMed Central PMCID: PMC2957927.
164. Mariussen E. Neurotoxic effects of perfluoroalkylated compounds: mechanisms of action and environmental relevance. *Archives of toxicology*. 2012;86(9):1349-67. Epub 2012/03/30. doi: 10.1007/s00204-012-0822-6. PubMed PMID: 22456834.
165. Yang SN, Hsieh CC, Kuo HF, Lee MS, Huang MY, Kuo CH, et al. The effects of environmental toxins on allergic inflammation. *Allergy Asthma Immunol Res*. 2014;6(6):478-84. doi: 10.4168/aair.2014.6.6.478. PubMed PMID: 25374746; PubMed Central PMCID: PMC4214967.
166. Mathur PP, D'Cruz SC. The effect of environmental contaminants on testicular function. *Asian J Androl*. 2011;13(4):585-91. doi: 10.1038/aja.2011.40. PubMed PMID: 21706039; PubMed Central PMCID: PMC3739630.
167. Schober W, Lubitz S, Belloni B, Gebauer G, Lintelmann J, Matuschek G, et al. Environmental polycyclic aromatic hydrocarbons (PAHs) enhance allergic inflammation by acting on human basophils. *Inhalation toxicology*. 2007;19 Suppl 1:151-6. doi: 10.1080/08958370701496046. PubMed PMID: 17886062.

168. Liu D, Perkins JT, Petriello MC, Hennig B. Exposure to coplanar PCBs induces endothelial cell inflammation through epigenetic regulation of NF-kappaB subunit p65. *Toxicol Appl Pharmacol.* 2015;289(3):457-65. doi: 10.1016/j.taap.2015.10.015. PubMed PMID: 26519613; PubMed Central PMCID: PMC4662647.
169. Mathur PP, Huang L, Kashour A, Vaithinathan S, Agarwal A. Environmental toxicants and testicular apoptosis. *the Open Reproductive Science Journal.* 2011;3:114-24.
170. Vetrano AM, Laskin DL, Archer F, Syed K, Gray JP, Laskin JD, et al. Inflammatory effects of phthalates in neonatal neutrophils. *Pediatr Res.* 2010;68(2):134-9. doi: 10.1203/00006450-201011001-00260
10.1203/PDR.0b013e3181e5c1f7. PubMed PMID: 20453712; PubMed Central PMCID: PMC2908957.
171. Malaguarnera G, Cataudella E, Giordano M, Nunnari G, Chisari G, Malaguarnera M. Toxic hepatitis in occupational exposure to solvents. *World J Gastroenterol.* 2012;18(22):2756-66. doi: 10.3748/wjg.v18.i22.2756. PubMed PMID: 22719183; PubMed Central PMCID: PMC3374978.
172. Kerr JF, Wyllie AH, Currie AR. Apoptosis: a basic biological phenomenon with wide-ranging implications in tissue kinetics. *Br J Cancer.* 1972;26(4):239-57. PubMed PMID: 4561027; PubMed Central PMCID: PMC2008650.
173. Ptak G, Zacchini F, Czernik M, Fidanza A, Palmieri C, Della Salda L, et al. A short exposure to polychlorinated biphenyls deregulates cellular autophagy in mammalian blastocyst in vitro. *Hum Reprod.* 2012;27(4):1034-42. doi: 10.1093/humrep/der454. PubMed PMID: 22298839.
174. Zhang Z, Miah M, Culbreth M, Aschner M. Autophagy in Neurodegenerative Diseases and Metal Neurotoxicity. *Neurochem Res.* 2016;41(1-2):409-22. doi: 10.1007/s11064-016-1844-x. PubMed PMID: 26869037.
175. Gebel T, Marchan R, Hengstler JG. The nanotoxicology revolution. *Archives of toxicology.* 2013;87(12):2057-62. Epub 2013/11/10. doi: 10.1007/s00204-013-1158-6. PubMed PMID: 24202081.
176. Nel A, Xia T, Madler L, Li N. Toxic potential of materials at the nanolevel. *Science.* 2006;311(5761):622-7. doi: 10.1126/science.1114397. PubMed PMID: 16456071.
177. Parkin J, Cohen B. An overview of the immune system. *Lancet.* 2001;357(9270):1777-89. doi: 10.1016/S0140-6736(00)04904-7. PubMed PMID: 11403834.
178. Genuis SJ. Sensitivity-related illness: the escalating pandemic of allergy, food intolerance and chemical sensitivity. *The Science of the Total Environment.* 2010;408(24):6047-61. Epub 2010/10/06. doi: 10.1016/j.scitotenv.2010.08.047. PubMed PMID: 20920818.
179. Moszczynski P, Rutowski J, Slowinski S, Bem S. Immunological effects of occupational exposure to metallic mercury in the population of T-cells and NK-cells. *Analyst.* 1998;123:99-103.
180. Li Q, Nagahara N, Takahashi H, Takeda K, Okumura K, Minami M. Organophosphorus pesticides markedly inhibit the activities of natural killer, cytotoxic T lymphocyte and lymphokine-activated killer: a proposed inhibiting mechanism via granzyme inhibition. *Toxicology.* 2002;172(3):181-90. PubMed PMID: 11893417.
181. Whalen MM, Loganathan BG, Yamashita N, Saito T. Immunomodulation of human natural killer cell cytotoxic function by triazine and carbamate pesticides. *Chem Biol Interact.* 2003;145(3):311-9. PubMed PMID: 12732457.
182. Saxena AK, Singh KP, Nagle SL, Gupta BN, Ray PK, Srivastav RK, et al. Effect of exposure to toxic gas on the population of Bhopal: Part IV--Immunological and chromosomal studies. *Indian J Exp Biol.* 1988;26(3):173-6. PubMed PMID: 3397120.
183. Nemery B. Late consequences of accidental exposure to inhaled irritants: RADS and the Bhopal disaster. *Eur Respir J.* 1996;9(10):1973-6. PubMed PMID: 8902452.

184. Shrivastava R. Bhopal Gas Disaster: Review on Health Effects of Methyl Isocyanate. *Research Journal of Environmental Sciences* 2011;5:150-6.
185. Pollard KM, Hultman P, Kono DH. Toxicology of autoimmune diseases. *Chem Res Toxicol.* 2010;23(3):455-66. doi: 10.1021/tx9003787. PubMed PMID: 20078109; PubMed Central PMCID: PMC3076021.
186. Miller FW, Alfredsson L, Costenbader KH, Kamen DL, Nelson LM, Norris JM, et al. Epidemiology of environmental exposures and human autoimmune diseases: findings from a National Institute of Environmental Health Sciences Expert Panel Workshop. *J Autoimmun.* 2012;39(4):259-71. doi: 10.1016/j.jaut.2012.05.002. PubMed PMID: 22739348; PubMed Central PMCID: PMC3496812.
187. Cai P, Konig R, Boor PJ, Kondraganti S, Kaphalia BS, Khan MF, et al. Chronic exposure to trichloroethene causes early onset of SLE-like disease in female MRL +/+ mice. *Toxicol Appl Pharmacol.* 2008;228(1):68-75. doi: 10.1016/j.taap.2007.11.031. PubMed PMID: 18234256; PubMed Central PMCID: PMC2442272.
188. Sobel ES, Gianini J, Butfiloski EJ, Croker BP, Schifffenbauer J, Roberts SM. Acceleration of autoimmunity by organochlorine pesticides in (N/ZB x NZW)F1 mice. *Environ Health Perspect.* 2005;113(3):323-8. PubMed PMID: 15743722; PubMed Central PMCID: PMC1253759.
189. Ezendam J, Vos JG, Pieters R. Research articles mechanisms of hexachlorobenzene-induced adverse immune effects in brown norway rats. *Journal of immunotoxicology.* 2005;1(3):167-75. doi: 10.1080/15476910490907026. PubMed PMID: 18958650.
190. Hultman P, Bell LJ, Enestrom S, Pollard KM. Murine susceptibility to mercury. I. Autoantibody profiles and systemic immune deposits in inbred, congenic, and intra-H-2 recombinant strains. *Clin Immunol Immunopathol.* 1992;65(2):98-109. PubMed PMID: 1395135.
191. Johansson U, Hansson-Georgiadis H, Hultman P. Murine silver-induced autoimmunity: silver shares induction of antinucleolar antibodies with mercury, but causes less activation of the immune system. *Int Arch Allergy Immunol.* 1997;113(4):432-43. PubMed PMID: 9250589.
192. Havarinasab S, Johansson U, Pollard KM, Hultman P. Gold causes genetically determined autoimmune and immunostimulatory responses in mice. *Clin Exp Immunol.* 2007;150(1):179-88. doi: 10.1111/j.1365-2249.2007.03469.x. PubMed PMID: 17680821; PubMed Central PMCID: PMC2219286.
193. Parks CG, Conrad K, Cooper GS. Occupational exposure to crystalline silica and autoimmune disease. *Environ Health Perspect.* 1999;107 Suppl 5:793-802. PubMed PMID: 10970168; PubMed Central PMCID: PMC1566238.
194. Otsuki T, Maeda M, Murakami S, Hayashi H, Miura Y, Kusaka M, et al. Immunological effects of silica and asbestos. *Cell Mol Immunol.* 2007;4(4):261-8. PubMed PMID: 17764616.
195. Blossom SJ, Pumford NR, Gilbert KM. Activation and attenuation of apoptosis of CD4+ T cells following in vivo exposure to two common environmental toxicants, trichloroacetaldehyde hydrate and trichloroacetic acid. *J Autoimmun.* 2004;23(3):211-20. doi: 10.1016/j.jaut.2004.06.007. PubMed PMID: 15501392.
196. Brown JM, Pfau JC, Pershouse MA, Holian A. Silica, apoptosis, and autoimmunity. *Journal of immunotoxicology.* 2005;1(3):177-87. PubMed PMID: 18958651.
197. Dahlgren J, Takhar H, Anderson-Mahoney P, Kotlerman J, Tarr J, Warshaw R. Cluster of systemic lupus erythematosus (SLE) associated with an oil field waste site: a cross sectional study. *Environ Health.* 2007;6:8. PubMed PMID: 17316448.
198. Markowitz SS, McDonald CJ, Fethiere W, Kerzner MS. Occupational acroosteolysis. *Arch Dermatol.* 1972;106(2):219-23. PubMed PMID: 4261762.

199. Rodnan GP, Benedek TG, Medsger TA, Jr., Cammarata RJ. The association of progressive systemic sclerosis (scleroderma) with coal miners' pneumoconiosis and other forms of silicosis. *Ann Intern Med.* 1967;66(2):323-34. PubMed PMID: 4224922.
200. Mak A, Tay SH. Environmental factors, toxicants and systemic lupus erythematosus. *Int J Mol Sci.* 2014;15(9):16043-56. doi: 10.3390/ijms150916043. PubMed PMID: 25216337; PubMed Central PMCID: PMC4200809.
201. Thompson PA, Khatami M, Baglolle CJ, Sun J, Harris SA, Moon EY, et al. Environmental immune disruptors, inflammation and cancer risk. *Carcinogenesis.* 2015;36 Suppl 1:S232-53. doi: 10.1093/carcin/bgv038. PubMed PMID: 26106141; PubMed Central PMCID: PMC4492068.
202. Bodin J, Stene LC, Nygaard UC. Can exposure to environmental chemicals increase the risk of diabetes type 1 development? *Biomed Res Int* 2015; doi: 10.1155/2015/208947.
203. Genuis SJ. Chemical Sensitivity: Pathophysiology or Pathopsychology? . *Clinical therapeutics* 2013; 35 (5.):572-7.
204. Miller CS. Toxicant-induced loss of tolerance--an emerging theory of disease? *Environ Health Perspect.* 1997;105 Suppl 2:445-53. PubMed PMID: 9167978.
205. De Luca C, Scordo MG, Cesareo E, Pastore S, Mariani S, Maiani G, et al. Biological definition of multiple chemical sensitivity from redox state and cytokine profiling and not from polymorphisms of xenobiotic-metabolizing enzymes. *Toxicol Appl Pharmacol.* 2010. Epub 2010/05/01. doi: S0041-008X(10)00144-4 [pii] 10.1016/j.taap.2010.04.017. PubMed PMID: 20430047.
206. Belpomme D, Campagnac C, Irigaray P. Reliable disease biomarkers characterizing and identifying electrohypersensitivity and multiple chemical sensitivity as two etiopathogenic aspects of a unique pathological disorder. *Rev Environ Health.* 2015;30(4):251-71. doi: 10.1515/reveh-2015-0027. PubMed PMID: 26613326.
207. Jedrychowski W, Perera F, Maugeri U, Miller RL, Rembiesz M, Flak E, et al. Intrauterine exposure to lead may enhance sensitization to common inhalant allergens in early childhood: a prospective prebirth cohort study. *Environmental Research.* 2011;111(1):119-24. Epub 2010/11/26. doi: 10.1016/j.envres.2010.11.002. PubMed PMID: 21094490; PubMed Central PMCID: PMC3026073.
208. Reichrtova E, Ciznar P, Prachar V, Palkovicova L, Veningerova M. Cord serum immunoglobulin E related to the environmental contamination of human placentas with organochlorine compounds. *Environmental health perspectives.* 1999;107(11):895-9. Epub 1999/11/02. PubMed PMID: 10544157; PubMed Central PMCID: PMC1566702.
209. Environmental Working Group. Body burden - the pollution in newborns: A benchmark investigation of industrial chemicals, pollutants and pesticides in umbilical cord blood. (Executive Summary) July 14, 2005. [Accessed Sept 16, 2005] <http://ewg.org/reports/bodyburden2/execsumm.php>.
210. Jedrychowski W, Galas A, Pac A, Flak E, Camman D, Rauh V, et al. Prenatal ambient air exposure to polycyclic aromatic hydrocarbons and the occurrence of respiratory symptoms over the first year of life. *Eur J Epidemiol.* 2005;20(9):775-82. PubMed PMID: 16170661.
211. Stolevik SB, Nygaard UC, Namork E, Haugen M, Kvalem HE, Meltzer HM, et al. Prenatal exposure to polychlorinated biphenyls and dioxins is associated with increased risk of wheeze and infections in infants. *Food and chemical toxicology : an international journal published for the British Industrial Biological Research Association.* 2011;49(8):1843-8. Epub 2011/05/17. doi: 10.1016/j.fct.2011.05.002. PubMed PMID: 21571030.
212. Grandjean P, Poulsen LK, Heilmann C, Steuerwald U, Weihe P. Allergy and sensitization during childhood associated with prenatal and lactational exposure to marine pollutants.

- Environmental health perspectives. 2010;118(10):1429-33. Epub 2010/06/22. doi: 10.1289/ehp.1002289. PubMed PMID: 20562055; PubMed Central PMCID: PMC2957924.
213. Okada E, Sasaki S, Saijo Y, Washino N, Miyashita C, Kobayashi S, et al. Prenatal exposure to perfluorinated chemicals and relationship with allergies and infectious diseases in infants. *Environmental Research*. 2012;112:118-25. Epub 2011/10/28. doi: 10.1016/j.envres.2011.10.003. PubMed PMID: 22030285.
214. Miyashita C, Sasaki S, Saijo Y, Washino N, Okada E, Kobayashi S, et al. Effects of prenatal exposure to dioxin-like compounds on allergies and infections during infancy. *Environmental Research*. 2011;111(4):551-8. Epub 2011/02/18. doi: 10.1016/j.envres.2011.01.021. PubMed PMID: 21324443.
215. Mishra PK, Dabadghao S, Modi GK, Desikan P, Jain A, Mittra I, et al. In utero exposure to methyl isocyanate in the Bhopal gas disaster: evidence of persisting hyperactivation of immune system two decades later. *Occup Environ Med*. 2009;66(4):279. doi: 10.1136/oem.2008.041517. PubMed PMID: 19295137.
216. Heo Y, Lee BK, Ahn KD, Lawrence DA. Serum IgE elevation correlates with blood lead levels in battery manufacturing workers. *Hum Exp Toxicol*. 2004;23(5):209-13. PubMed PMID: 15222397.
217. Islam LN, Nabi AH, Rahman MM, Zahid MS. Association of respiratory complications and elevated serum immunoglobulins with drinking water arsenic toxicity in human. *Journal of environmental science and health*. 2007;42(12):1807-14. doi: 10.1080/10934520701566777. PubMed PMID: 17952781.
218. Kovacova-Hanuszkova E, Buday T, Gavliakova S, Plevkova J. Histamine, histamine intoxication and intolerance. *Allergol Immunopathol (Madr)*. 2015;43(5):498-506. doi: 10.1016/j.aller.2015.05.001. PubMed PMID: 26242570.
219. Maintz L, Novak N. Histamine and histamine intolerance. *Am J Clin Nutr*. 2007;85(5):1185-96. PubMed PMID: 17490952.
220. Kern JK, Geier DA, Audhya T, King PG, Sykes LK, Geier MR. Evidence of parallels between mercury intoxication and the brain pathology in autism. *Acta Neurobiol Exp (Wars)*. 2012;72(2):113-53. PubMed PMID: 22810216.
221. Su X, Wellen KE, Rabinowitz JD. Metabolic control of methylation and acetylation. *Curr Opin Chem Biol*. 2016;30:52-60. doi: 10.1016/j.cbpa.2015.10.030. PubMed PMID: 26629854; PubMed Central PMCID: PMC4731252.
222. Bottiglieri T. Folate, vitamin B(1)(2), and S-adenosylmethionine. *Psychiatr Clin North Am*. 2013;36(1):1-13. doi: 10.1016/j.psc.2012.12.001. PubMed PMID: 23538072.
223. Huff MO, Todd SL, Smith AL, Elpers JT, Smith AP, Murphy RD, et al. Arsenite and Cadmium Activate MAPK/ERK via Membrane Estrogen Receptors and G-Protein Coupled Estrogen Receptor Signaling in Human Lung Adenocarcinoma Cells. *Toxicol Sci*. 2016;152(1):62-71. doi: 10.1093/toxsci/kfw064. PubMed PMID: 27071941.
224. Leeming RJ. The role of tetrahydrobiopterin in neurological disease: a review. *J Ment Defic Res*. 1981;25 Pt 4:231-41. PubMed PMID: 6120241.
225. Eggar C, Hamon CG, Morar C, Al-Salihi F, Blair JA, Barford PA. The effect of lead on tetrahydrobiopterin metabolism. A possible mechanism for neurotoxicity. *Clin Chim Acta*. 1986;161(1):103-9. PubMed PMID: 3815851.
226. Garcia-Arenas G, Claudio L, Perez-Severiano F, Rios C. Lead acetate exposure inhibits nitric oxide synthase activity in capillary and synaptosomal fractions of mouse brain. *Toxicol Sci*. 1999;50(2):244-8. PubMed PMID: 10478861.
227. Vaziri ND, Ding Y, Ni Z. Nitric oxide synthase expression in the course of lead-induced hypertension. *Hypertension*. 1999;34(4 Pt 1):558-62. PubMed PMID: 10523326.

228. Bandara SB, Eubig PA, Sadowski RN, Schantz SL. Developmental PCB Exposure Increases Audiogenic Seizures and Decreases Glutamic Acid Decarboxylase in the Inferior Colliculus. *Toxicol Sci.* 2016;149(2):335-45. doi: 10.1093/toxsci/kfv237. PubMed PMID: 26543103; PubMed Central PMCID: PMC4900216.
229. Santoro A, Ferrante MC, Di Guida F, Pirozzi C, Lama A, Simeoli R, et al. Polychlorinated Biphenyls (PCB 101, 153, and 180) Impair Murine Macrophage Responsiveness to Lipopolysaccharide: Involvement of NF-kappaB Pathway. *Toxicol Sci.* 2015;147(1):255-69. doi: 10.1093/toxsci/kfv127. PubMed PMID: 26141388.
230. Baquero F, Nombela C. The microbiome as a human organ. *Clin Microbiol Infect.* 2012;18 Suppl 4:2-4. doi: 10.1111/j.1469-0691.2012.03916.x. PubMed PMID: 22647038.
231. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, Gordon JI. The human microbiome project. *Nature.* 2007;449(7164):804-10. doi: 10.1038/nature06244. PubMed PMID: 17943116; PubMed Central PMCID: PMC3709439.
232. Parfrey LW, Walters WA, Knight R. Microbial eukaryotes in the human microbiome: ecology, evolution, and future directions. *Front Microbiol.* 2011;2:153. doi: 10.3389/fmicb.2011.00153. PubMed PMID: 21808637; PubMed Central PMCID: PMC3135866.
233. Lukes J, Stensvold CR, Jirku-Pomajbikova K, Wegener Parfrey L. Are Human Intestinal Eukaryotes Beneficial or Commensals? *PLoS Pathog.* 2015;11(8):e1005039. doi: 10.1371/journal.ppat.1005039. PubMed PMID: 26270819; PubMed Central PMCID: PMC4536199.
234. Goulet O. Potential role of the intestinal microbiota in programming health and disease. *Nutr Rev.* 2015;73 Suppl 1:32-40. doi: 10.1093/nutrit/nuv039. PubMed PMID: 26175488.
235. Ursell LK, Knight R. Xenobiotics and the human gut microbiome: metatranscriptomics reveal the active players. *Cell Metab.* 2013;17(3):317-8. doi: 10.1016/j.cmet.2013.02.013. PubMed PMID: 23473028; PubMed Central PMCID: PMC3641660.
236. Breton J, Massart S, Vandamme P, De Brandt E, Pot B, Foligne B. Ecotoxicology inside the gut: impact of heavy metals on the mouse microbiome. *BMC Pharmacol Toxicol.* 2013;14:62. Epub 2013/12/12. doi: 10.1186/2050-6511-14-62. PubMed PMID: 24325943; PubMed Central PMCID: PMC3874687.
237. Zhang S, Jin Y, Zeng Z, Liu Z, Fu Z. Subchronic Exposure of Mice to Cadmium Perturbs Their Hepatic Energy Metabolism and Gut Microbiome. *Chem Res Toxicol.* 2015;28(10):2000-9. doi: 10.1021/acs.chemrestox.5b00237. PubMed PMID: 26352046.
238. Han SJ, Ha KH, Jeon JY, Kim HJ, Lee KW, Kim DJ. Impact of Cadmium Exposure on the Association between Lipopolysaccharide and Metabolic Syndrome. *Int J Environ Res Public Health.* 2015;12(9):11396-409. doi: 10.3390/ijerph120911396. PubMed PMID: 26378560; PubMed Central PMCID: PMC4586682.
239. Dheer R, Patterson J, Dudash M, Stachler EN, Bibby KJ, Stolz DB, et al. Arsenic induces structural and compositional colonic microbiome change and promotes host nitrogen and amino acid metabolism. *Toxicol Appl Pharmacol.* 2015;289(3):397-408. doi: 10.1016/j.taap.2015.10.020. PubMed PMID: 26529668; PubMed Central PMCID: PMC4662606.
240. Ottman N, Smidt H, de Vos WM, Belzer C. The function of our microbiota: who is out there and what do they do? *Front Cell Infect Microbiol.* 2012;2:104. doi: 10.3389/fcimb.2012.00104. PubMed PMID: 22919693; PubMed Central PMCID: PMC3417542.
241. Cucchiara S, Iebba V, Conte MP, Schippa S. The microbiota in inflammatory bowel disease in different age groups. *Dig Dis.* 2009;27(3):252-8. doi: 10.1159/000228558. PubMed PMID: 19786749.

242. Konstantynowicz J, Porowski T, Zoch-Zwierz W, Wasilewska J, Kadziela-Olech H, Kulak W, et al. A potential pathogenic role of oxalate in autism. *Eur J Paediatr Neurol*. 2012;16(5):485-91. doi: 10.1016/j.ejpn.2011.08.004. PubMed PMID: 21911305.
243. Jonassen JA, Cao LC, Honeyman T, Scheid CR. Mechanisms mediating oxalate-induced alterations in renal cell functions. *Crit Rev Eukaryot Gene Expr*. 2003;13(1):55-72. PubMed PMID: 12839097.
244. Farooq SM, Boppana NB, Devarajan A, Sekaran SD, Shankar EM, Li C, et al. C-phycoyanin confers protection against oxalate-mediated oxidative stress and mitochondrial dysfunctions in MDCK cells. *PLoS One*. 2014;9(4):e93056. doi: 10.1371/journal.pone.0093056. PubMed PMID: 24691130; PubMed Central PMCID: PMC3972226.
245. Veena CK, Josephine A, Preetha SP, Rajesh NG, Varalakshmi P. Mitochondrial dysfunction in an animal model of hyperoxaluria: a prophylactic approach with fucoidan. *Eur J Pharmacol*. 2008;579(1-3):330-6. doi: 10.1016/j.ejphar.2007.09.044. PubMed PMID: 18001705.
246. Bagga HS, Chi T, Miller J, Stoller ML. New insights into the pathogenesis of renal calculi. *Urol Clin North Am*. 2013;40(1):1-12. doi: 10.1016/j.ucl.2012.09.006. PubMed PMID: 23177630; PubMed Central PMCID: PMC4165395.
247. Betts KS. A study in balance: how microbiomes are changing the shape of environmental health. *Environ Health Perspect*. 2011;119(8):A340-6. doi: 10.1289/ehp.119-a340. PubMed PMID: 21807598; PubMed Central PMCID: PMC3237378.
248. Arrieta MC, Stiemsma LT, Amenyogbe N, Brown EM, Finlay B. The intestinal microbiome in early life: health and disease. *Front Immunol*. 2014;5:427. doi: 10.3389/fimmu.2014.00427. PubMed PMID: 25250028; PubMed Central PMCID: PMC4155789.
249. Mattila E, Uusitalo-Seppala R, Wuorela M, Lehtola L, Nurmi H, Ristikankare M, et al. Fecal transplantation, through colonoscopy, is effective therapy for recurrent *Clostridium difficile* infection. *Gastroenterology*. 2012;142(3):490-6. doi: 10.1053/j.gastro.2011.11.037. PubMed PMID: 22155369.
250. O'Horo JC, Jindai K, Kunzer B, Safdar N. Treatment of recurrent *Clostridium difficile* infection: a systematic review. *Infection*. 2014;42(1):43-59. doi: 10.1007/s15010-013-0496-x. PubMed PMID: 23839210; PubMed Central PMCID: PMC3934353.
251. National Institute of Environmental Health Sciences: Division of Extramural Research and Training Cellular OaSPB. Microbiome/Environment Interactions. , <http://www.niehs.nih.gov/news/newsletter/2012/3/spotlight-council/file62863.pdf>. 2012.
252. Ganesan K, Raza SK, Vijayaraghavan R. Chemical warfare agents. *J Pharm Bioallied Sci*. 2010;2(3):166-78. doi: 10.4103/0975-7406.68498. PubMed PMID: 21829312; PubMed Central PMCID: PMC3148621.
253. Togo F, Takahashi M. Heart rate variability in occupational health --a systematic review. *Ind Health*. 2009;47(6):589-602. PubMed PMID: 19996534.
254. Cobb CO, Sahmarani K, Eissenberg T, Shihadeh A. Acute toxicant exposure and cardiac autonomic dysfunction from smoking a single narghile waterpipe with tobacco and with a "healthy" tobacco-free alternative. *Toxicol Lett*. 2012;215(1):70-5. doi: 10.1016/j.toxlet.2012.09.026. PubMed PMID: 23059956; PubMed Central PMCID: PMC3641895.
255. Folino AF, Scapellato ML, Canova C, Maestrelli P, Bertorelli G, Simonato L, et al. Individual exposure to particulate matter and the short-term arrhythmic and autonomic profiles in patients with myocardial infarction. *Eur Heart J*. 2009;30(13):1614-20. doi: 10.1093/eurheartj/ehp136. PubMed PMID: 19411666.
256. Coghlan S, Horder J, Inkster B, Mendez MA, Murphy DG, Nutt DJ. GABA system dysfunction in autism and related disorders: from synapse to symptoms. *Neuroscience and*

- biobehavioral reviews. 2012;36(9):2044-55. Epub 2012/07/31. doi: 10.1016/j.neubiorev.2012.07.005. PubMed PMID: 22841562.
257. Arakawa O, Nakahiro M, Narahashi T. Mercury modulation of GABA-activated chloride channels and non-specific cation channels in rat dorsal root ganglion neurons. *Brain Res.* 1991;551(1-2):58-63. PubMed PMID: 1717106.
258. Lasley SM, Gilbert ME. Rat hippocampal glutamate and GABA release exhibit biphasic effects as a function of chronic lead exposure level. *Toxicological Sciences.* 2002;66(1):139-47.
259. Werbach M. *Foundations of Nutritional Medicine: A Sourcebook of Clinical Research.* Tarzana, CA: Third Line Press 1997.
260. Kjellstrom T. Mechanism and epidemiology of bone effects of cadmium. *IARC Sci Publ.* 1992;(118):301-10. PubMed PMID: 1303956.
261. Moss M. Drugs as anti-nutrients. *Journal of Nutritional & Environmental Medicine.* 2007;16(2):149-66.
262. Latar I, Koufany M, Hablot J, Loeuille D, Netter P, Jouzeau JY, et al. Association between rheumatoid arthritis and systemic mastocytosis: a case report and literature review. *Clin Rheumatol* 2016.
263. Frenzel L, Hermine O. Mast cells and inflammation. *Joint Bone Spine.* 2013;80(2):141-5. doi: 10.1016/j.jbspin.2012.08.013. PubMed PMID: 23116710.
264. Conti P, Kempuraj D. Important role of mast cells in multiple sclerosis. *Mult Scler Relat Disord.* 2016;5:77-80. doi: 10.1016/j.msard.2015.11.005. PubMed PMID: 26856948.
265. Kenna TJ, Brown MA. The role of IL-17-secreting mast cells in inflammatory joint disease. *Nat Rev Rheumatol.* 2013;9(6):375-9. doi: 10.1038/nrrheum.2012.205. PubMed PMID: 23229447.
266. Walker ME, Hatfield JK, Brown MA. New insights into the role of mast cells in autoimmunity: evidence for a common mechanism of action? *Biochim Biophys Acta.* 2012;1822(1):57-65. doi: 10.1016/j.bbadis.2011.02.009. PubMed PMID: 21354470; PubMed Central PMCID: PMC4424662.
267. Xu Y, Chen G. Mast cell and autoimmune diseases. *Mediators Inflamm.* 2015;2015:246126. doi: 10.1155/2015/246126. PubMed PMID: 25944979; PubMed Central PMCID: PMC4402170.
268. Boeckxstaens G. Mast cells and inflammatory bowel disease. *Curr Opin Pharmacol.* 2015;25:45-9. doi: 10.1016/j.coph.2015.11.005. PubMed PMID: 26629596.
269. Shih AR, Deshpande V, Ferry JA, Zukerberg L. Clinicopathologic Characteristics of Systemic Mastocytosis in the Intestine. *Histopathology.* 2016. doi: 10.1111/his.13033. PubMed PMID: 27391777.
270. Regauer S. Mast cell activation syndrome in pain syndromes bladder pain syndrome/interstitial cystitis and vulvodinia. *Transl Androl Urol.* 2016;5(3):396-7. doi: 10.21037/tau.2016.03.12. PubMed PMID: 27297031; PubMed Central PMCID: PMC4893522.
271. Afrin LB. Mast cell activation disease and the modern epidemic of chronic inflammatory disease. *Transl Res.* 2016;174:33-59. doi: 10.1016/j.trsl.2016.01.003. PubMed PMID: 26850903.
272. Schedle A, Samorapoompichit P, Fureder W, Rausch-Fan XH, Franz A, Sperr WR, et al. Metal ion-induced toxic histamine release from human basophils and mast cells. *J Biomed Mater Res.* 1998;39(4):560-7. PubMed PMID: 9492216.
273. Kempuraj D, Asadi S, Zhang B, Manola A, Hogan J, Peterson E, et al. Mercury induces inflammatory mediator release from human mast cells. *J Neuroinflammation.* 2010;7:20. doi: 10.1186/1742-2094-7-20. PubMed PMID: 20222982; PubMed Central PMCID: PMC2850891.

274. Shim J, Kennedy RH, Weatherly LM, Hutchinson LM, Pelletier JH, Hashmi HN, et al. Arsenic inhibits mast cell degranulation via suppression of early tyrosine phosphorylation events. *J Appl Toxicol*. 2016. doi: 10.1002/jat.3300. PubMed PMID: 27018130.
275. Yasunaga S, Nishi K, Nishimoto S, Sugahara T. Methoxychlor enhances degranulation of murine mast cells by regulating FcεRI-mediated signal transduction. *Journal of immunotoxicology*. 2015;12(3):283-9. doi: 10.3109/1547691X.2014.962122. PubMed PMID: 25418051.
276. Nakamura R, Teshima R, Sawada J. Effect of dialkyl phthalates on the degranulation and Ca²⁺ response of RBL-2H3 mast cells. *Immunol Lett*. 2002;80(2):119-24. PubMed PMID: 11750043.
277. O'Brien E, Dolinoy DC, Mancuso P. Bisphenol A at concentrations relevant to human exposure enhances histamine and cysteinyl leukotriene release from bone marrow-derived mast cells. *Journal of immunotoxicology*. 2014;11(1):84-9. doi: 10.3109/1547691X.2013.800925. PubMed PMID: 23782309; PubMed Central PMCID: PMC4030600.
278. Urb M, Pouliot P, Gravelat FN, Olivier M, Sheppard DC. *Aspergillus fumigatus* induces immunoglobulin E-independent mast cell degranulation. *J Infect Dis*. 2009;200(3):464-72. doi: 10.1086/600070. PubMed PMID: 19527167.
279. Niide O, Suzuki Y, Yoshimaru T, Inoue T, Takayama T, Ra C. Fungal metabolite gliotoxin blocks mast cell activation by a calcium- and superoxide-dependent mechanism: implications for immunosuppressive activities. *Clin Immunol*. 2006;118(1):108-16. doi: 10.1016/j.clim.2005.08.012. PubMed PMID: 16213796.
280. Jandacek RJ, Anderson N, Liu M, Zheng S, Yang Q, Tso P. Effects of yo-yo diet, caloric restriction, and olestra on tissue distribution of hexachlorobenzene. *American journal of physiology*. 2005;288(2):G292-9. PubMed PMID: 15513954.
281. Knox EG. Childhood cancers and atmospheric carcinogens. *J Epidemiol Community Health*. 2005;59(2):101-5.
282. Hauser R, Williams P, Altshul L, Calafat AM. Evidence of interaction between polychlorinated biphenyls and phthalates in relation to human sperm motility. *Environ Health Perspect*. 2005;113(4):425-30.
283. Ashby J, Houthoff E, Kennedy SJ, Stevens J, Bars R, Jekat FW, et al. The challenge posed by endocrine-disrupting chemicals. *Environ Health Perspect*. 1997;105(2):164-9.
284. Anyanwu EC, Campbell AW, Vojdani A. Neurophysiological effects of chronic indoor environmental toxic mold exposure on children. *ScientificWorldJournal*. 2003;3:281-90.
285. Khattak S, Moghtader GK, McMartin K, Barrera M, Kennedy D, Koren G. Pregnancy outcome following gestational exposure to organic solvents: a prospective controlled study. *JAMA*. 1999;281:1106-9.
286. Genuis SJ. Toxic causes of mental illness are overlooked. *Neurotoxicology*. 2008;29(6):1147-9. PubMed PMID: 18621076.
287. Genuis SJ. Elimination of persistent toxicants from the human body. *Human & experimental toxicology*. 2011;30(1):3-18. Epub 2010/04/20. doi: 10.1177/0960327110368417. PubMed PMID: 20400489.
288. Genuis SJ, Liu H, Genuis QIT, Martin JW. Phlebotomy treatment for elimination of perfluoroalkyl acids in a highly exposed family: a retrospective case-series. *PLoS One*. 2014;In Press.
289. Ross GH, Sternquist MC. Methamphetamine exposure and chronic illness in police officers: significant improvement with sauna-based detoxification therapy. *Toxicology and industrial health*. 2012. Epub 2011/11/18. doi: 10.1177/0748233711425070. PubMed PMID: 22089658.

290. Genuis SJ, Birkholz D, Rodushkin I, Beeson S. Blood, Urine, and Sweat (BUS) Study: Monitoring and Elimination of Bioaccumulated Toxic Elements. *Arch Environ Contam Toxicol* 2010. Epub 2010/11/09. doi: 10.1007/s00244-010-9611-5. PubMed PMID: 21057782.
291. Bernhoft RA. Cadmium toxicity and treatment. *ScientificWorldJournal*. 2013;2013:394652. doi: 10.1155/2013/394652. PubMed PMID: 23844395; PubMed Central PMCID: PMC3686085.
292. Mayo Clinic Laboratories. Testosterone, Total, Bioavailable, and Free, Serum. available and accessed Aug 14,2016 at [<http://www.mayomedicallaboratories.com/test-catalog/Clinical+and+Interpretive/83686>]. 2016.
293. Dynacare-Gamma Laboratory Partnership. Estradiol. Accessed August 14, 2016 at [<https://www.dynacare.ca/specialpages/secondarynav/find-a-test/nat/estradiol.aspx?sr=ont&st=estradiol&>]. 2016.
294. Engelmann J, Janke V, Volk J, Leyhausen G, von Neuhoff N, Schlegelberger B, et al. Effects of BisGMA on glutathione metabolism and apoptosis in human gingival fibroblasts in vitro. *Biomaterials*. 2004;25(19):4573-80. Epub 2004/05/04. doi: 10.1016/j.biomaterials.2003.11.048. PubMed PMID: 15120502.
295. Lin RY, Smith AJ, Hergenroeder P. High serum albuterol levels and tachycardia in adult asthmatics treated with high-dose continuously aerosolized albuterol. *Chest*. 1993;103(1):221-5. PubMed PMID: 8417883.
296. Brenner PF, Goebelsmann U, Stanczyk FZ, Mishell DR, Jr. Serum levels of ethinylestradiol following its ingestion alone or in oral contraceptive formulations. *Contraception*. 1980;22(1):85-95. PubMed PMID: 7418409.
297. United States Senate committee on environment and public works: Subcommittee on superfund toxics and environmental health. Current science on public exposures to toxic chemicals. Accessed Dec 21/2014 at [<https://www.hsdl.org/?view&did=29623>]. 2010.
298. Mayo Clinic Laboratories. Paroxetine, Serum, Clinical Information, Accessed August 14, 2016 at [http://www.mayomedicallaboratories.com/interpretive-guide/?alpha=P&unit_code=83731]. 2016.
299. City of Ottawa. Lemieux Island Water Purification Plant,. 2015 Drinking Water Quality physical, microbiological, chemical, & radiological test results. Accessed August 14, 2016 at [http://documents.ottawa.ca/sites/documents.ottawa.ca/files/documents/2015_WQSummaryTable_Lemieux_en.pdf]. 2015.

