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Stephen J. Genuis & Edmond Kyrillos

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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)

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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.

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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)

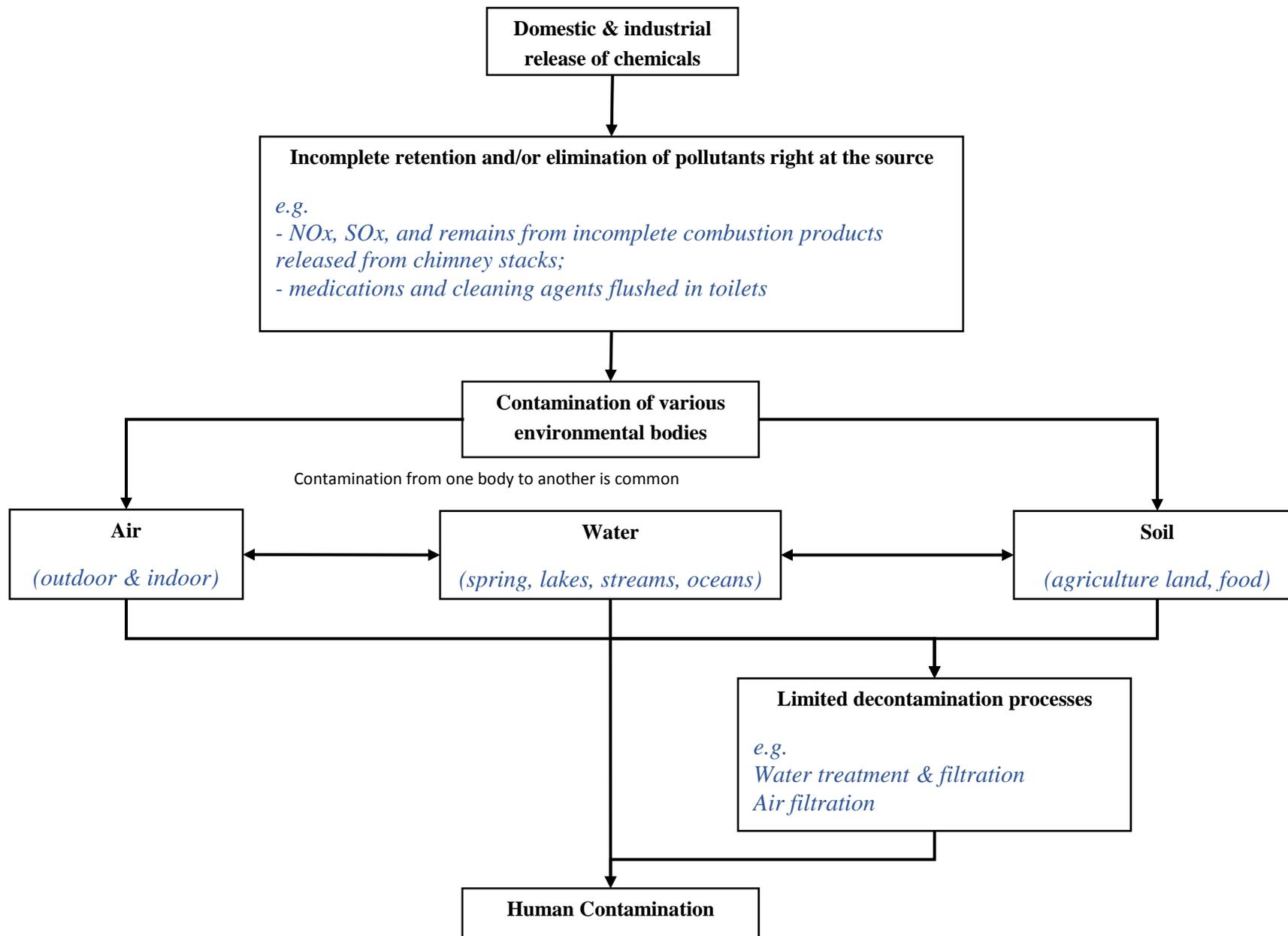


Figure 2 – Overview of exogenous toxicant passage from the environment through the human body.

(Body wastes are not included.)

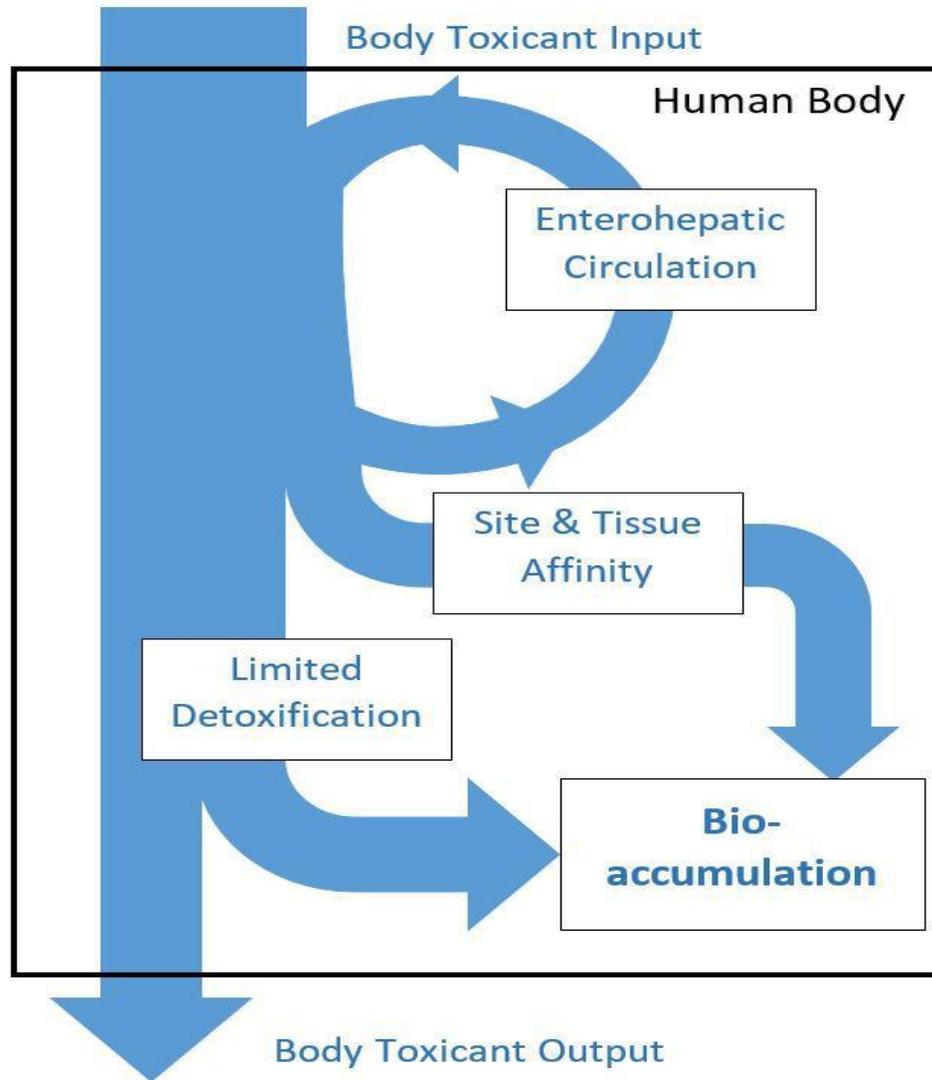


Figure 3 – Pathway to clinical disease.

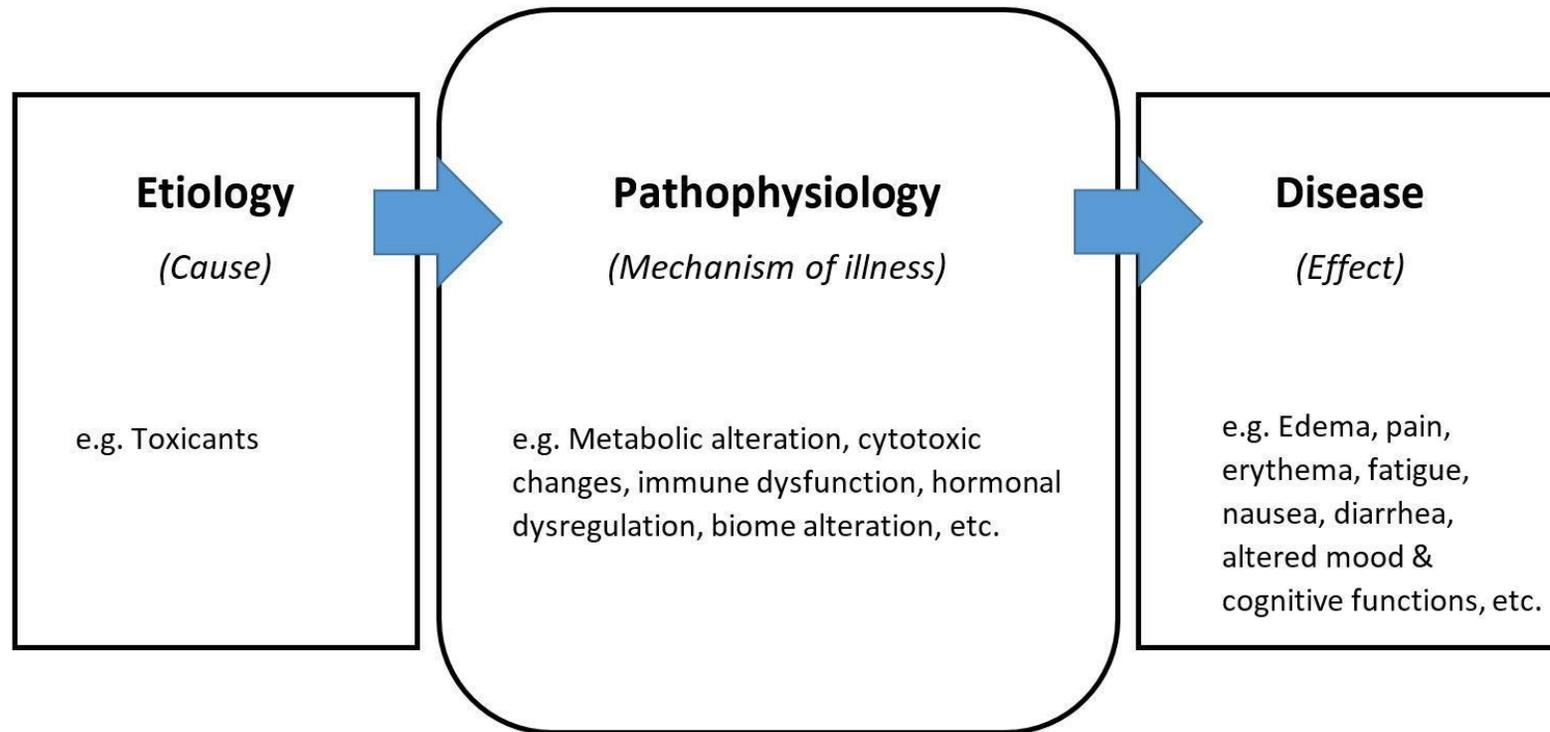


Figure 4 – Simplified overview of the main steps involved in the elimination of intrinsic waste products of metabolism, xenobiotics and toxicants.

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

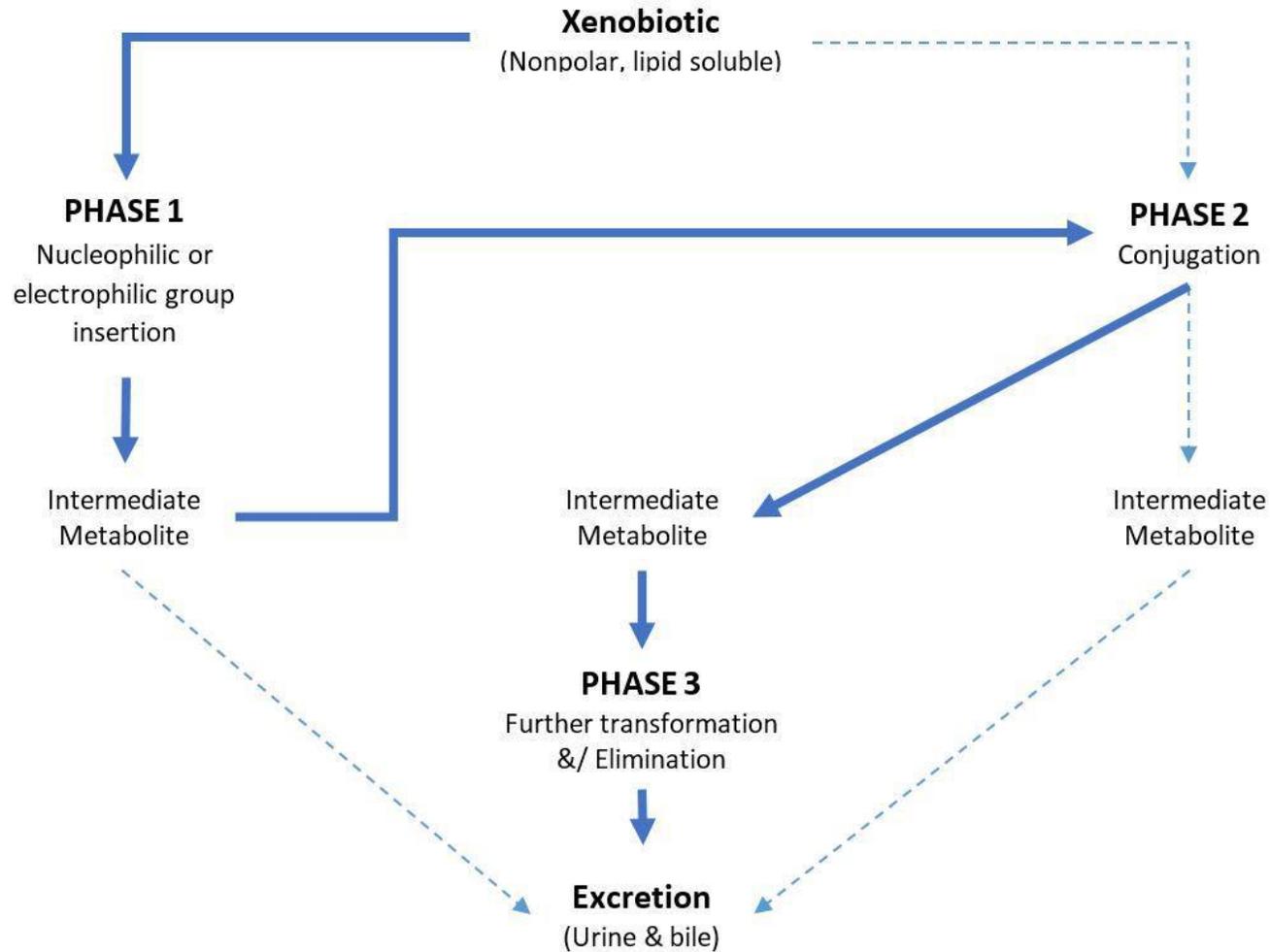


Figure 5 – Simplified overview of main mechanisms of cellular and extracellular toxicity.
(ER = Endoplasmic reticulum)

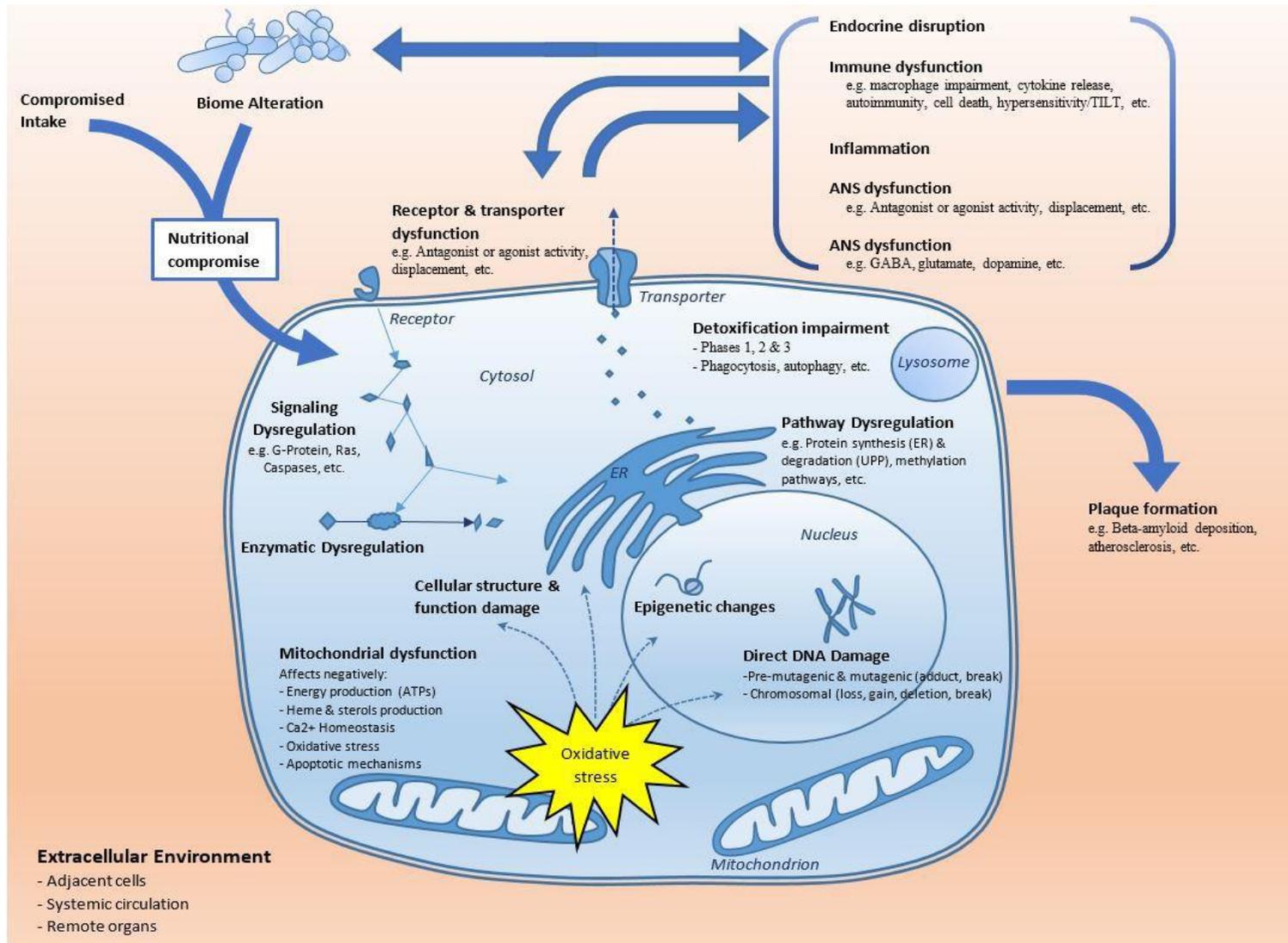


Figure 6 –Endocrine disruption and receptor dysregulation.

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.

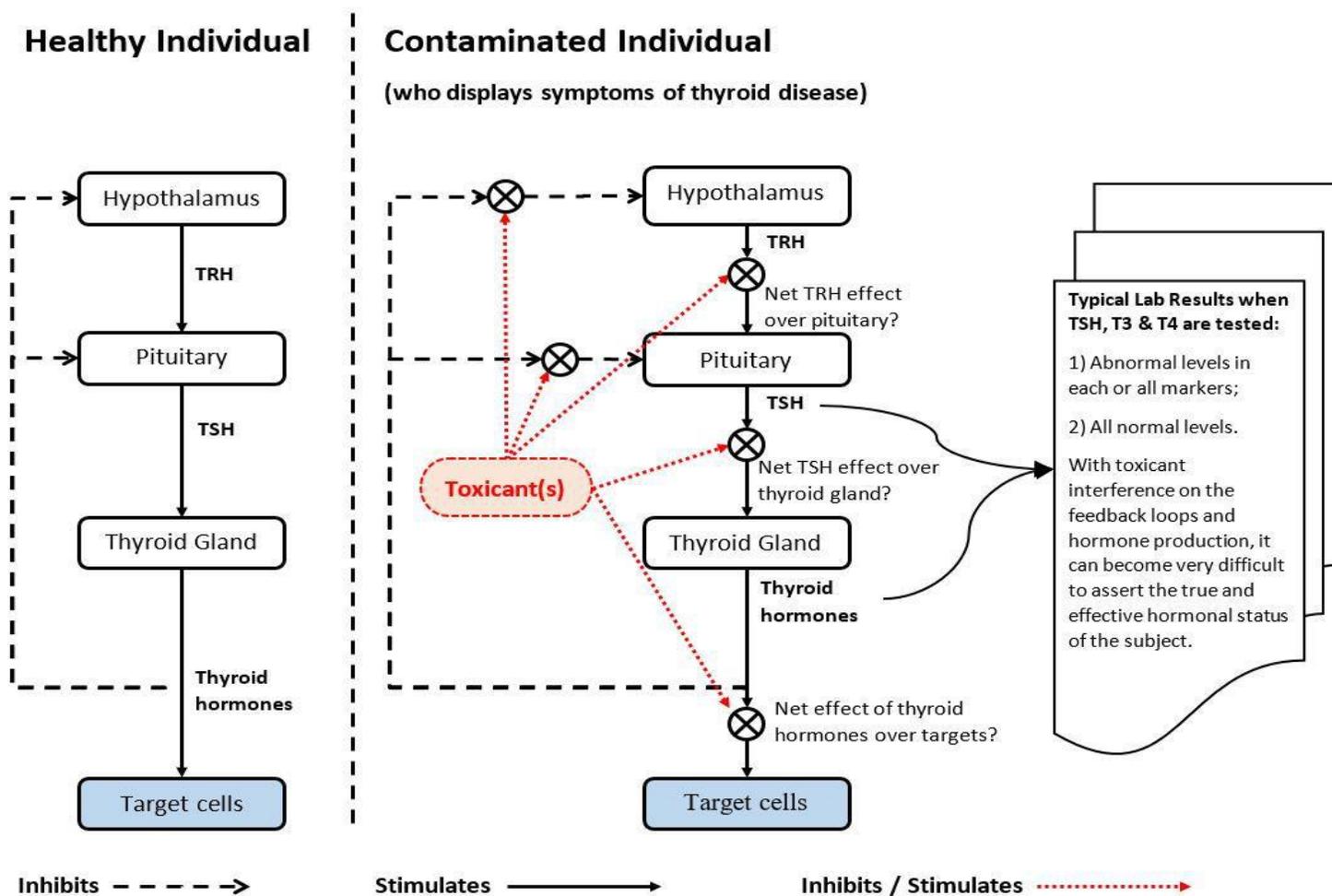
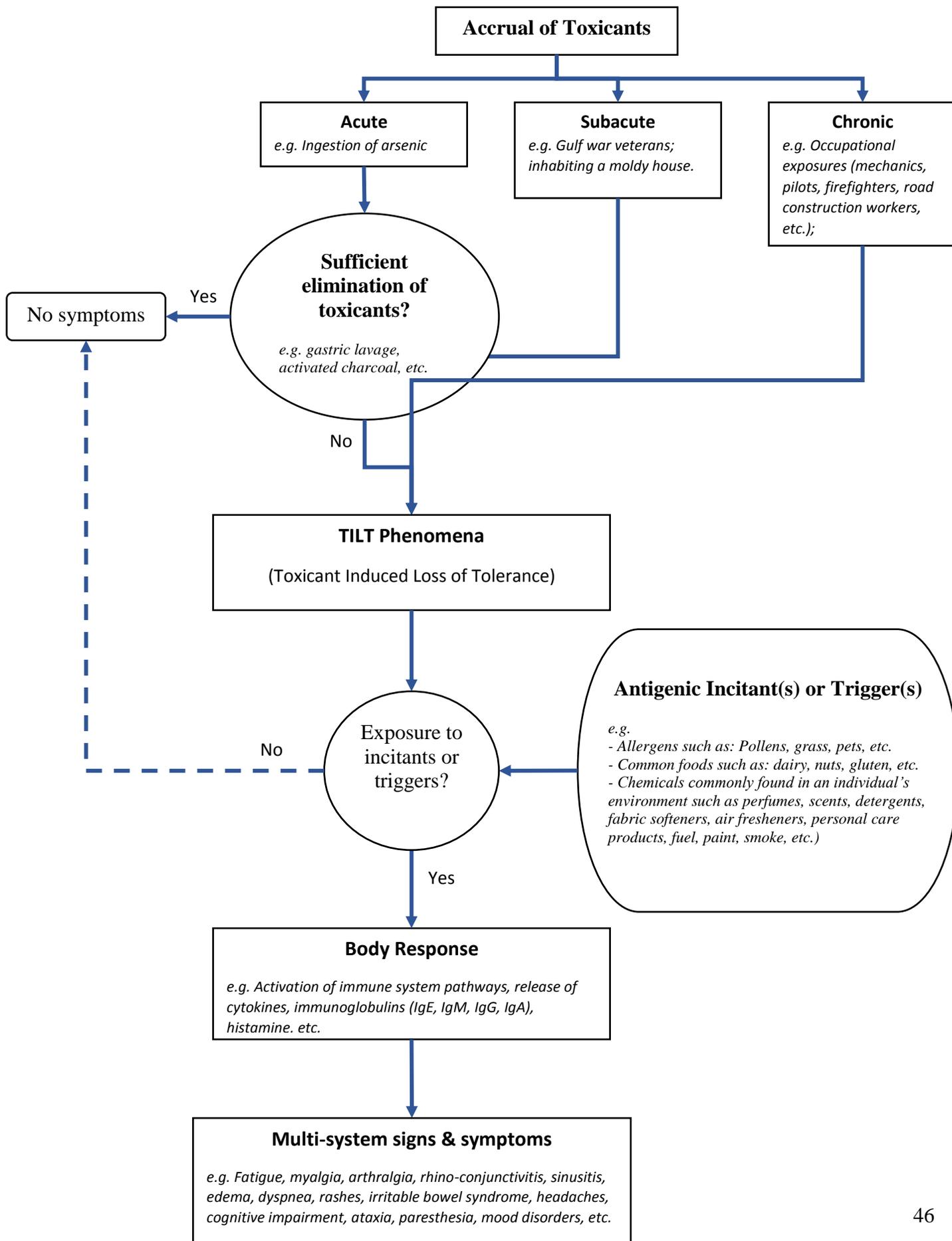


Figure 7 – Toxicant induced loss of tolerance (TILT) phenomena. As a result of toxicant bioaccumulation within the body, the immune system becomes oversensitive and responds to low dose levels of common environmental chemicals (e.g. perfume) or chemical structures (e.g. pollen) to which the same individual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



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