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REVIEW ARTICLE

The chemical disruption of human metabolism

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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.

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Biochemistry; chemical agents; toxicants; epigenetics; endocrine disruption; sensitivity-related illness; detoxification pathways; metabolic pathways; metabolism; multimorbidity; mitochondria; oxidative stress; immune dysfunction

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

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 (NHANES 2012; Di Renzo et al. 2015) (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 (Centers for Disease Control and Prevention: Department of Health and Human Services 2013; Health Canada 2013) primarily because of (i) ongoing reabsorption in the enterohepatic circulation (Jandacek & Genuis 2013), (ii) limited detoxification capabilities of humans compared to other species (Rat Genome Sequencing Project C 2004), 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 (Welshons et al. 2003).

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 (Welshons et al. 2003; Canfield et al. 2003), with incremental influence for many pollutants at increasing levels of accrual (Frisbee et al. 2010; Steenland et al. 2010). 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

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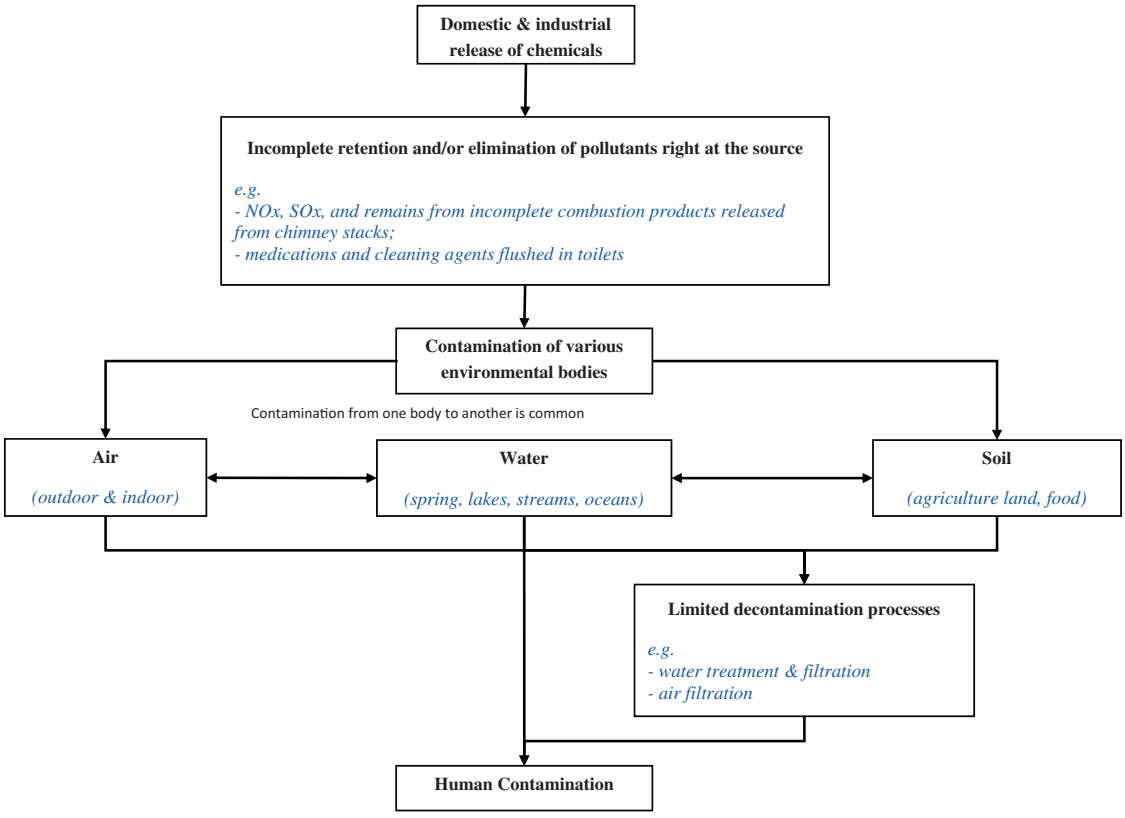

Figure 1. Environmental contamination. NO_x : nitrogen oxide compounds; SO_x: sulfur oxide compounds.

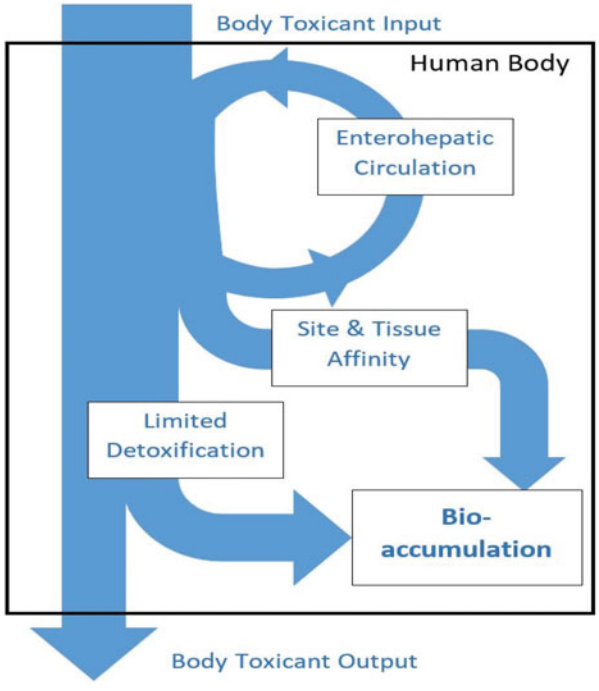

Figure 2. Overview of exogenous toxicant passage from the environment through the human body (body wastes are not included).

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.

From etiology to clinical symptoms

On one hand, 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 (Genuis 2005).

Throughout history, conversely, much focus has been devoted to the study of disease etiology or 'what's out there making us sick?' (Genuis 2012). 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

Table 1. Examples of physiologically active levels for some common hormones, toxicants, and pharmacological compounds for comparative purposes (Brenner et al. 1980; Lin et al. 1993; Engelmann et al. 2004; Steenland et al. 2010, United States Senate Committee on Environment and Public Works: Subcommittee on Superfund Toxics and Environmental Health 2010; City of Ottawa 2016, Gamma-Dynacare Laboratory Partnership 2016; Mayo Clinic Laboratories 2016a,b). Uric acid (serum) reference range for adult males is 3.7–8.0 mg/dL (220–476 μmole/L), and 2.7–6.1 mg/dL for women (160–363 μmole/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 H_2O 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)	>4000 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

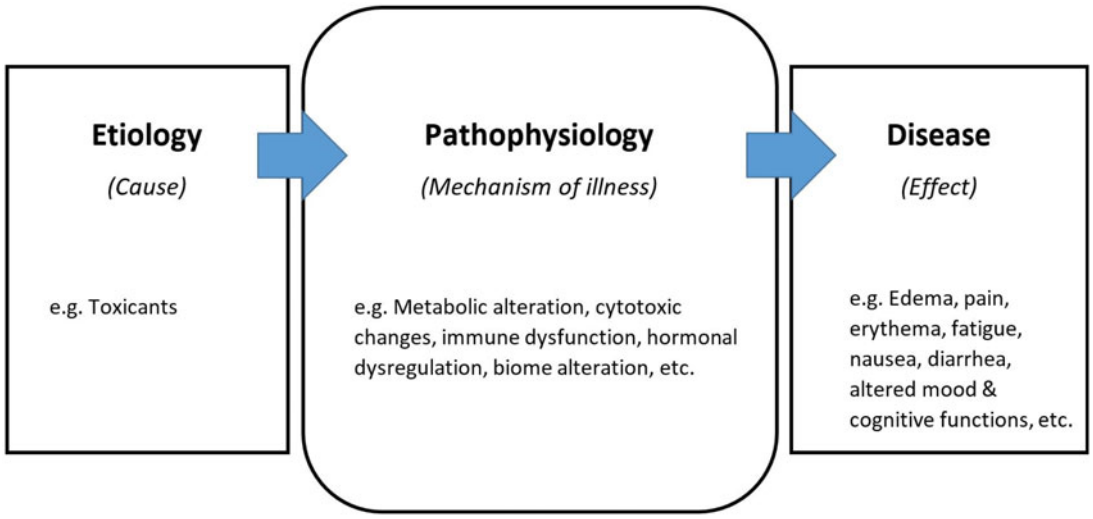

Figure 3. Pathway to clinical disease.

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 (Horton 2005; Perrin et al. 2007).

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 (Genuis 2008). 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 (Genuis 2012). 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 (Baker 2003; Genuis 2012). The Centre for Disease Control recently confirmed that virtually all illness is the result of genomic predisposition in combination with environmental factors (Office of Genomics and Disease Prevention: Centers for Disease Control and Prevention 2000) 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 (Rappaport & Smith 2010). Other publications in the literature also confirm the enormous contribution of environmental determinants to the etiology of specific chronic diseases (Selmi et al. 2012; Wu et al. 2016). A predominant environmental factor long ago identified and confirmed to be a consistent determinant of illness is exposure to toxic chemical agents (Crone 2004).

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 (Crone 2004). 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 (Welshons et al. 2003; Genuis et al. 2013). In this paper, we will discuss much of what the recent scientific literature has elucidated with regard to toxic chemical exposures and the mechanisms by which these agents induce metabolic disruption and ultimately clinical illness.

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 (Dijkers 2009). 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

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 (Takser et al. 2005; Crofton 2008; Shen *et al.* 2009; Brent 2010).

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

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 (Crofton 2008; Brent 2010) (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.

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 (Pritchard 1979; Cascio et al. 2012), at the level of various organelles (such as the nucleus, mitochondria, and/or endoplasmic reticulum), and anywhere in between in the cytosol (Waseem & Parvez 2013). 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 (Van Houten et al. 2006; Chavan & Krishnamurthy 2012; Kumar et al. 2012; Langie et al. 2015). Furthermore, interference with enzyme expression (O'Shaughnessy et al. 2011; Al-Mousa & Michelangeli 2012) 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.

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 phenoxy-herbicide families all demonstrate human genotoxic propensity with impact involving one or more of the above mentioned genotoxic modes of action (Garry et al. 1996; Gomez-Arroyo et al. 2000; Lander et al. 2000; Zeljezic & Garaj-Vrhovac 2002; Grover et al. 2003).

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 (Zhang et al. 2008; Kitamura & Hiramatsu 2010; Yen et al. 2012) and several pesticide compounds (Chinta et al. 2008; Hossain & Richardson 2011; Pesonen et al. 2012) induce disturbance of ER homeostasis and function, including the aggregation of misfolded proteins (Mostafalou & Abdollahi 2013; Chen et al. 2014). 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 (Mostafalou & Abdollahi 2013).

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 (Rossignol & Frye 2014) to cancer (Seyfried 2015). 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 (Orrenius et al. 2011). Mitochondrial injury can also lead to the production of reactive oxygen species (ROS) and to consequent alteration of mitochondrial DNA (Meyer et al. 2013), 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 (Orrenius et al. 2011). Brominated flame retardants are examples of specific xenochemicals that can inflict considerable cytotoxic damage on mitochondria (Van Houten et al. 2006; Al-Mousa & Michelangeli 2012).

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.

Oxidative stress

Oxidative stress refers to the corrosive and toxic impact that occurs when there is an imbalance between the production of ROS 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 (Pearson & Patel 2016), inflammation (Haberzettl et al. 2016), carcinogenesis (Klaunig & Kamendulis 2004), 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 (Singh et al. 1995; Sakac & Sakac 2000; James et al. 2004; Kennedy et al. 2005; Valko et al. 2006, 2007; Arican & Kurutas 2008; Bonomini et al. 2008; Jomova et al. 2010; Hwang 2013; Ramond et al. 2013; Pohanka 2014; Joseph et al. 2015).

The overproduction of ROS 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 (Upham & Wagner 2001; Valko et al. 2007; Jomova et al. 2010). Such radical species have the potential to disrupt many cell functions and can induce gene mutation and expression (Klaunig & Kamendulis 2004). Certain heavy metals, for instance, can mediate the formation of reactive species (Valko et al. 2005) 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 (Valko et al. 2005), and various modifications to DNA bases (Sahnoun et al. 1997; Sakac & Sakac 2000; Jomova et al. 2010; Jomova & Valko 2011). Nanoparticles of certain chemical agents such as titanium dioxide may also produce ROS (Cui et al. 2014). 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 (Liu et al. 2007; Doi & Uetsuka 2011).

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 (Sakac & Sakac 2000), and the production of mutagenic and carcinogenic toxins (Valko et al. 2005; Jomova et al. 2010), It is also evident that some chemical toxicants, including various chemotherapeutic agents (Victorino et al. 2014), 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 (Gu & Manautou 2012).

Peroxynitrite (PXN)

One reactive nitrogen species that merits particular attention and that may be formed in response to common chemical exposures such as benzene (Lippmann 2009) as well as other toxicants (Roberts et al. 2010; O'Neill et al. 2011; Sorrenti et al. 2013) is 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 (Pacher et al. 2007; Calcerrada et al. 2011). 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 (Pacher et al. 2007; Islam et al. 2015). It is thought by some that ongoing PXN-related destruction may be a determinant of many chronic diseases of modern civilization (Pacher et al. 2007). 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 (Hooper et al. 2000), and other agents such as molecular hydrogen which may therapeutically serve to

diminish PXN-related damage (Ohta 2014; Ichihara et al. 2015).

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 (Crofton 2008; Brent 2010; Vuong et al. 2015).

The literature abounds with examples of toxicant induced receptor dysregulation. For example, polychlorinated biphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) have been found to act as agonists or antagonists of thyroid receptors and alter levels of thyroxine and TSH (Brent 2010). 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 (Shen et al. 2009) 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 (Mariussen & Fonnum 2003; Stavenes Andersen et al. 2009). As the major excitatory brain neurotransmitter, glutamate enhancing effects may lead to induced neuro-excitotoxicity.

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 (Mostafalou & Abdollahi 2013). Some epigenetic changes serve to suppress normal gene expression, while other changes may facilitate the activation of genes (Relton & Davey Smith 2010; Hou et al. 2012). Recent evidence confirms that epigenetic alterations may serve as a basis for chronic illness and that such alterations can be transmitted to subsequent generations (Anway & Skinner 2008; Skinner 2011; Mostafalou & Abdollahi 2013).

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 methytransferase into 5-methylcytosine and has the effect of suppressing gene expression (Hou et al. 2012). 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 (Relton & Davey Smith 2010; Hou et al. 2012).

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 (Mostafalou & Abdollahi 2013). DNA methylation aberrations following exposure to dioxins have been linked to immune suppression (McClure et al. 2011) and various cancers (Dammann et al. 2010). Epigenetic modifications due to toxic metal exposure have been identified in children living in polluted areas (Bitto et al. 2014). Histone changes following exposure to neurotoxic insecticides were found to promote apoptosis and induce neurodegenerative changes (Anway & Skinner 2008). Epigenetic alterations are increasingly being linked to various other states including Parkinson's, Alzheimer's, ALS, multiple sclerosis, diabetes, and atherosclerosis, and even longevity (Anway & Skinner 2008; Gravina & Vijg 2010).

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 (Mizuno et al. 2003). Cells have specific enzymes that recognize and remove intrinsic chemical wastes and non-specific enzymes that can attach to xenobiotics to tag them with polar groups that facilitate active transport and cellular excretion (Jakoby & Ziegler 1990). The process of transforming and eliminating xenobiotic is referred to as 'detoxification' and is classically divided into three biotransformation phases (Omiecinski et al. 2011; Zmrzljak & Rozman 2012): phase 1 (bioactivation),

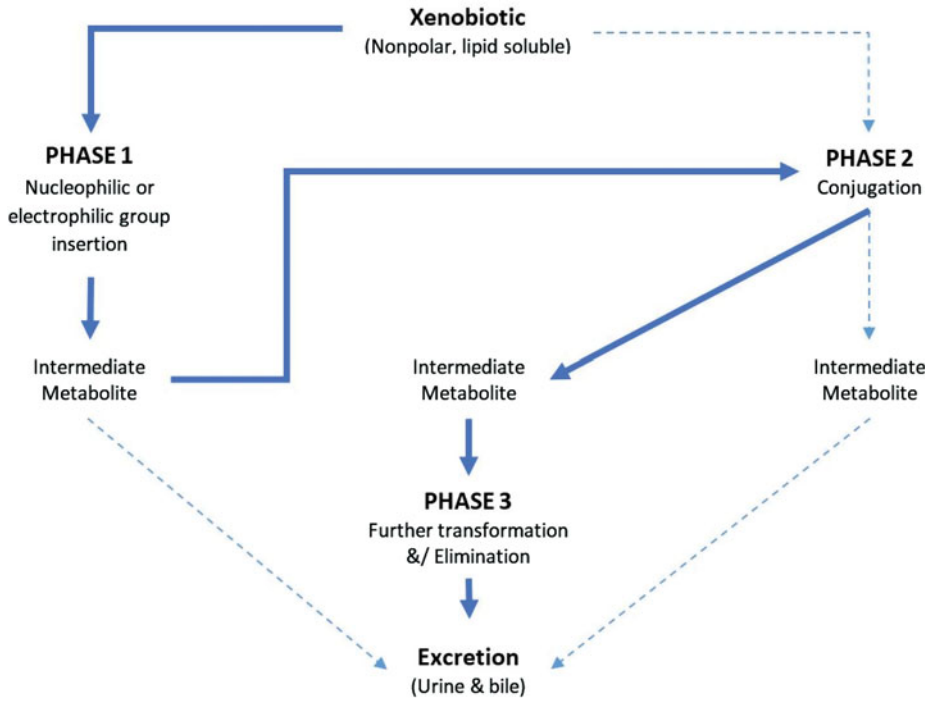

Figure 4. Simplified overview of the main steps involved in the elimination of intrinsic waste products of metabolism, xenobiotics, and toxicants (dashed lines represent short cuts that some compounds may take).

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 (Schlichting et al. 2000).

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 (Guengerich 2001; Liston et al. 2001; Schlichting et al. 2000; Gilbert et al. 2006). Phase 1 is mainly composed of cytochrome P450 enzymes regulated by nuclear receptors (Guengerich 2001; Strolin Benedetti 2011; Johnson et al. 2012; Zmrzljak & Rozman 2012) 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 (Homolya et al. 2003; Omiecinski et al. 2011). Phase 2 involves enzymes such as methyl-transferases, sulfo-transferases, glucoronosyl-transferases, glutathione *S*-transferase, and reactions remain intracellular (Jakoby & Ziegler 1990; Liston et al. 2001). 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 (Commandeur et al. 1995; Omiecinski et al. 2011).

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 (Omiecinski et al. 2011), 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 (Nicklisch et al. 2016).

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 (Johnson et al. 2012). For example, the ubiquitous pesticide agent glyphosate is reported to impair cytochromes P450 enzymes (Samsel & Seneff 2013), and lead was found to impair conjugation and elimination of some polycyclic aromatic hydrocarbons (PAHs) (Katsnelson et al. 2014; Varaksin et al. 2014). 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 (Giordano et al. 2008).

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 (Stefanis 2012). 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 (Jadiya and Nazir 2012; Dardiotis et al. 2013; Navarro-Yepes et al. 2016; Chin-Chan et al. 2015; Naughton et al. 2017).

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 (Yegambaram et al. 2015). 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 (Yegambaram et al. 2015). BFRs, widespread among consumer products, are pollutants that are known for their ability to cross blood–brain barriers and bioaccumulate in humans (Hakk & Letcher 2003; Al-Mousa & Michelangeli 2014), and to exhibit cytotoxic impact at low micromolar concentrations (Al-Mousa & Michelangeli 2012). 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 (Al-Mousa & Michelangeli 2012). 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 (Chin-Chan et al. 2015).

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 (Ramos et al. 1994).

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 so 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 (Omaye 2002). 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 (Pittman, 2012) 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 (Brent 2010). Cadmium has also been found to displace zinc in many metallo-enzymes and at DNA–zinc binding sites (Kim et al. 2015).

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 signaling and the finely tuned turning on and off of assorted biochemical pathways (Kass et al. 1990). Toxicants interfering with this process will potentially impair the necessary signaling 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 (Mostafalou & Abdollahi 2013). 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 (Li et al. 2007).

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 (Salome et al. 2015; Tramutola et al. 2016). This UPP pathway may be impacted by certain toxic elements (Yu et al. 2010) and

pesticide agents (Mostafalou & Abdollahi 2013; Rhodes et al. 2013).

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 (Nicklisch et al. 2016). 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 (Nicklisch et al. 2016).

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 (Orrenius et al. 2011 2013; Dagda et al. 2013), including various pesticides (Song et al. 2015; Wu et al. 2015).

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 (Orrenius et al. 2011). 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.

Endocrine disruption

The field of study surrounding endocrine disruption by chemical toxicants is burgeoning (Kabir et al. 2015; Maqbool et al. 2016). Endocrine disruption occurs when toxic

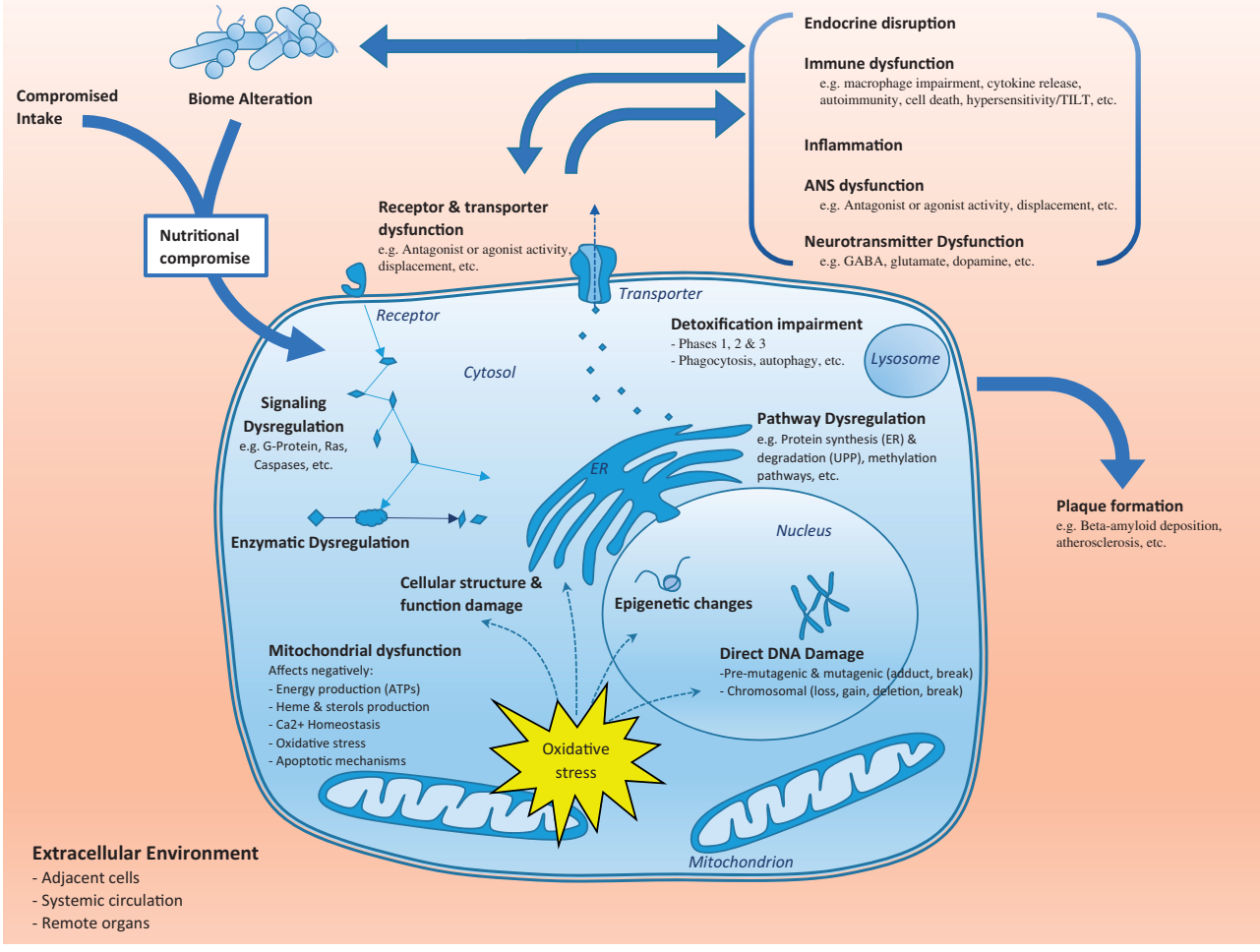

Figure 5. Simplified overview of main mechanisms of cellular and extracellular toxicity. ER: endoplasmic reticulum.

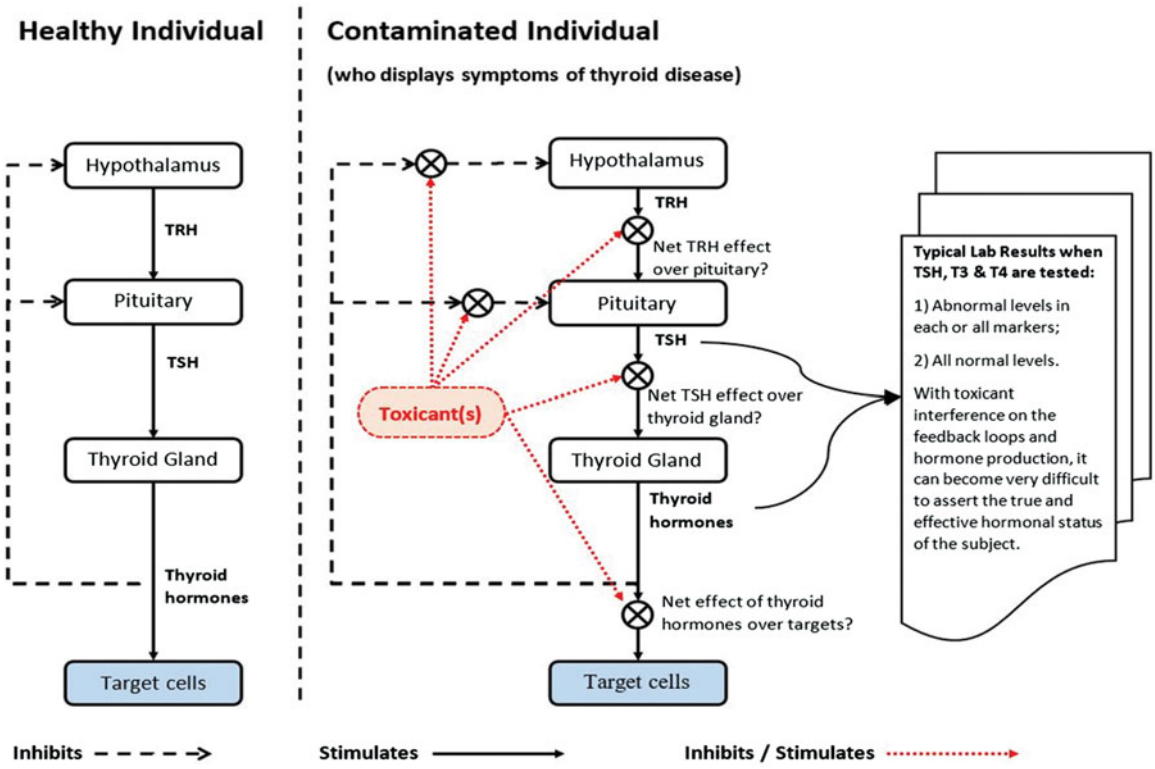

Figure 6. Endocrine disruption and receptor dysregulation. A simplified model of thyroid hormone feedback is used to illustrate the concept. Toxicants can have various disruptive effects and alter hormone synthesis, expression and reception. Phthalates have shown antagonist thyroid receptor activity while PCBs and PBDEs have shown both agonist and antagonist activity on thyroid receptors.

compounds are found to act with impact on hormone receptors as mentioned, but also when they interfere with organ response and feedback loops (The Prague Declaration on Endocrine Disruption 2005; Mnif et al. 2011; Mostafalou & Abdollahi 2013) (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 (Hendriks et al. 2010; Mostafalou & Abdollahi 2013) of various endocrine feedback systems with a spectrum of clinical manifestations (World Health Organization 2012; Kabir et al. 2015). 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 (Hendriks et al. 2010; World Health Organization 2012; Mostafalou & Abdollahi 2013). 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 (Skinner et al. 2011; Guerrero-Bosagna & Skinner 2012, 2014).

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 (Welshons et al. 2003). 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 sequealae 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 (Takser et al. 2005; Crofton 2008; Shen et al. 2009; Brent 2010).

Examples from the scientific literature of the clinical and public health impact of endocrine altering agents are too numerous to recount (World Health Organization 2012; Kabir et al. 2015; Maqbool et al. 2016) as many categories of compounds, such as perfluorinated compounds (Jensen & Leffers 2008), BPA and phthalates (Colon et al. 2000; Rubin 2011), various pesticides (Gray et al. 1999; Aguilar-Garduno et al. 2013), PCBs and dioxins (Birnbaum 1994), paraben preservatives (Final amended report on the safety assessment of Methylparaben, Ethylparaben, Propylparaben, Isopropylparaben, Butylparaben, Isobutylparaben, and Benzylparaben as used in cosmetic products 2008), acrylamide (Camacho et al. 2012), several mycotoxin (Frizzell et al. 2013a,b), and many toxic elements such as cadmium display hormone disrupting behavior (Takiguchi & Yoshihara 2006; Kortenkamp 2011). EDC-related sex ratio imbalances, for example, resulting in fewer male offspring in humans have been associated with bioaccumulation of some dioxins and pesticides (World Health Organization 2012). Phthalates and organochlorine pesticides are common toxicants that have been linked to an increased prevalence of fibroids (World Health Organization 2012). Phthalates, PCBs, and dioxins have been associated with endometriosis (World Health Organization 2012). Mixtures of chemicals with anti-

androgenic properties such as phthalates or a range of fungicides and pesticides during pregnancy increase the risk of cryptorchidism in the male newborn and other congenital abnormalities (World Health Organization 2012). Recent discussion has explored the impact of endocrine disruption on gender issues, sexual preference, and sexual behavior (Hood 2005; Balthazart 2011). 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 (Chevrier et al. 2010; Mariussen 2012; Maqbool et al. 2016) (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 (World Health Organization 2012). In review, the potential impact of endocrine altering hormones is vast and continues to be researched.

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 (Yang et al. 2014), (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 (Orrenius et al. 2011). Cellular signaling pathways such as the mitogen-activated protein kinase and stress-activated protein kinase cascades have also been shown to be activated and induce inflammation (Orrenius et al. 2011). 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 (Schober et al. 2007; Vetrano et al. 2010; Mathur and D'Cruz 2011; Mathur et al. 2011; Malaguarnera et al. 2012; Liu et al. 2015).

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 (Orrenius et al. 2011). For instance, it is known that efficient phagocytosis of dead or dying cells prevents the development of inflammation during apoptosis (Kerr et al. 1972); 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 (Ptak et al. 2012; Zhang et al. 2016) and inflammation may no longer be avoided (Orrenius et al. 2011).

Over the last decade, research related to the emerging production of nanoparticles has spawned the field of nanotoxicology (Gebel et al. 2013). Some nanoparticles, for example, have been found to induce autophagy, apoptosis, or necrosis and produce ROS leading to increased oxidative stress and inflammation (Nel et al. 2006).

Immune dysfunction

The immune system is a complex interactive network of lymphoid organs, specialized defense 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 (Parkin & Cohen 2001). 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 (Genuis 2010).

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 *defense* against tumors and viruses (Moszczynski et al. 1998; Li et al. 2002; Whalen et al. 2003). 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 (Saxena et al. 1988; Nemery 1996; Shrivastava 2011).

Autoimmunity

Increasing research has begun to suggest that chemical exposure can produce autoimmune manifestations in human populations and promote the development of autoimmunity (Pollard et al. 2010; Miller et al. 2012; Selmi et al. 2012). Human and animal research has confirmed the link between chemical exposure and autoimmune pathology for agents including solvents (Miller et al. 2012) such as trichloroethylene (Gilbert et al. 2006; Cai et al. 2008), some pesticides such as hexachlorobenzene (Sobel et al. 2005; Ezendam et al. 2005), various inorganic metals (Hultman et al. 1992; Johansson et al. 1997; Havarinasab et al. 2007), and other exposures including silica (Parks et al. 1999) and asbestos (Otsuki et al. 2007). In mice experimentation with trichlororethylene, 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 (Blossom et al. 2004). 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 (Rodnan et al. 1967; Markowitz et al. 1972; Brown et al. 2005; Dahlgren et al. 2007). Smokers have also been found to be at higher risk of seropositive rheumatoid arthritis (Miller et al. 2012).

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, pristine, phytane), and crystalline silica are determinants of autoimmune diseases (Brown et al. 2005; Dahlgren et al. 2007; Pollard et al. 2010; Mak & Tay 2014; Bodin et al. 2015).

Loss of tolerance/hypersensitivity

Recent evidence has also linked toxicant exposure and bioaccumulation with the pathogenesis of various hypersensitivity states (Genuis 2010). 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 (Genuis 2010; Genuis 2013).

Evidence increasingly suggests that such conditions may be immune-related through a mechanism called TILT or a toxicant induced loss of tolerance (Genuis 2010 2013; Miller 1997). The TILT model, first described by Miller (Miller 1997) (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 with control populations (De Luca et al. 2010). Emerging research on this SRI state confirms that elevated nitrotyrosine (a peroxynitrite marker) is a potential disease biomarker for this condition (Belpomme et al. 2015) – 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 (Genuis 2010).

Other studies have found correlations between pediatric allergies and prenatal exposure to toxicants through vertical transmission (Reichrtova et al. 1999; Jedrychowski et al. 2011), the latter being an increasingly common observation in perinatal medicine (Di Renzo et al. 2015; Environmental Working Group 2015). While elevations in IgE were correlated with organochloride placental contamination (Reichrtova et al. 1999), respiratory symptoms in the newborn were observed with prenatal maternal exposures to polycyclic aromatic hydrocarbons (PAHs), PCBs and dioxins (Jedrychowski et al. 2005; Stolevik et al. 2011) and allergies were triggered in children of mothers exposed to marine pollutants, lead, PFCs, and dioxin-like compounds (Jedrychowski et al. 2011; Grandjean et al. 2010; Miyashita et al. 2011). Hypersensitivity was also a common and enduring finding two decades later among children born of mothers exposed in the Bhopal tragedy (Mishra et al. 2009).

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 (Heo et al. 2004; Islam et al. 2007), 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 (Kovacova-Hanuskova et al. 2015; Maintz & Novak 2007).

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 (Johnson et al. 2012; Kumar et al. 2012). 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 (Kern et al. 2012). Mercury, for example, has the potential to impair glutamic acid decarboxylase (GAD) (Kern et al. 2012) 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

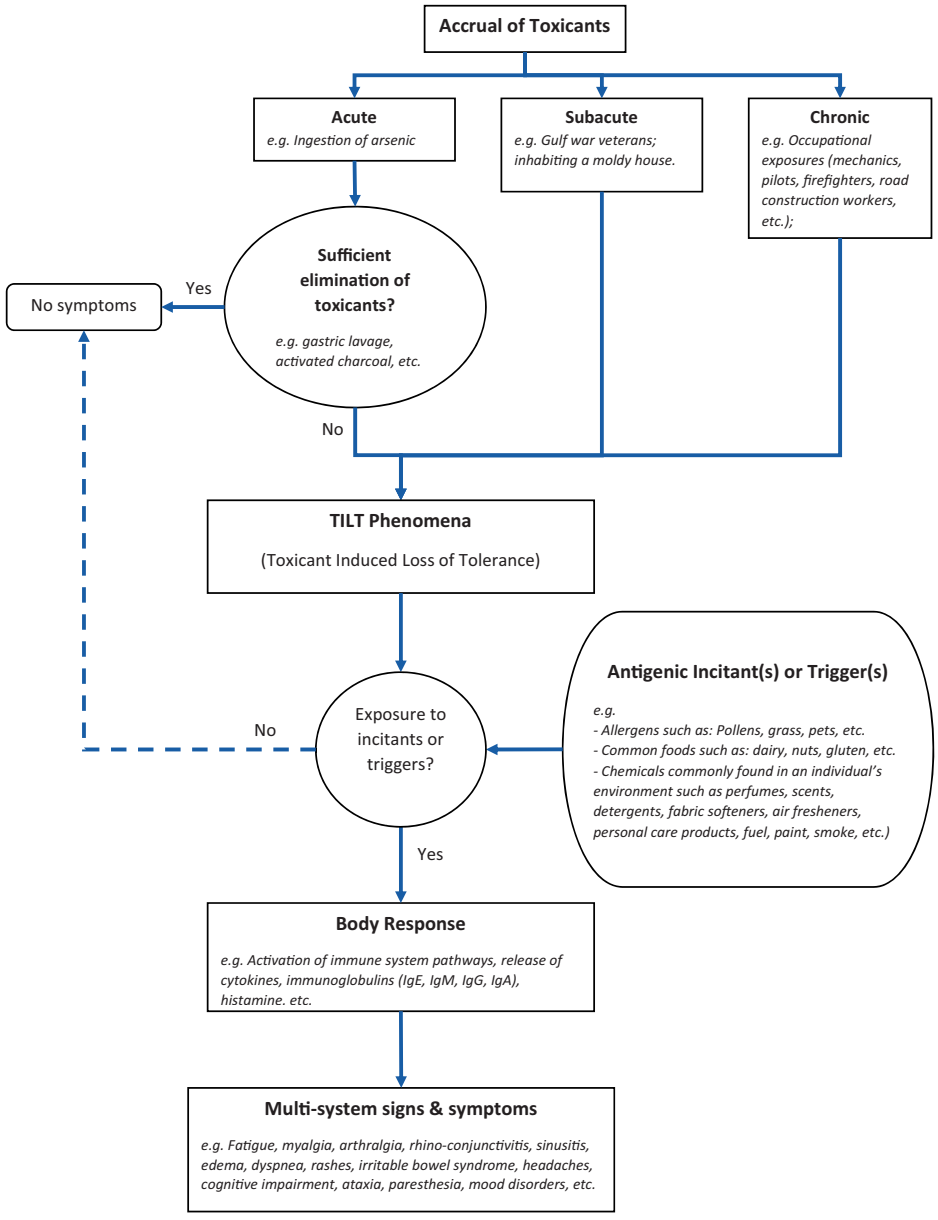

Figure 7. Toxicant induced loss of tolerance (TILT) phenomena. As a result of toxicant bioaccumulation within the body, the immune system becomes oversensitive and responds to low dose levels of common environmental chemicals (e.g. perfume) or chemical structures (e.g. pollen) to which the same individual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

disrupt the basic process of methylation in cells (Kern et al. 2012) required for over 150 metabolic processes including DNA repair, genetic expression, production of some neurotransmitters, and so on (Bottiglieri 2013; Su et al. 2016). Cadmium and arsenic have been shown to stimulate mitogen-activated protein kinase phosphorylation (Huff et al. 2016). 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 (Leeming 1981) and lead (Eggar et al. 1986). Another important example of enzymatic distortion with profound potential consequence is the impact of lead on nitric oxide synthase (NOS) activity (Garcia-Arenas et al. 1999). Lead contamination can interfere with the production of nitric oxide (Vaziri et al. 1999), 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. (O'Shaughnessy et al. 2011) were able to demonstrate that fetuses exposed to toxicants displayed a significantly altered expression of mRNA transcripts for liver enzymes. Animals exposed to PCBs have also demonstrated decreased levels of the enzyme GAD and manifested audiogenic seizures (Bandara et al. 2016). 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 (Santoro et al. 2015).

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 single nucleotide polymorphisms (SNPs) 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.

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 (Turnbaugh et al. 2007; Baquero & Nombela 2012). This biome includes various types of organisms including viruses, helminths, prokaryotes, and eukaryotes (Parfrey et al. 2011; Lukes et al. 2015). 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 (Goulet 2015). The importance of the biome as a determinant of health is so significant that some authors refer to it as 'the 11th organ system' (Baquero & Nombela 2012; Ursell & Knight 2013).

Common environmental chemicals (such as chlorine, heavy metals, assorted pesticides, and antibiotics) are found to interfere with microbiome viability and functionality – with potentially adverse clinical outcomes (Samsel & Seneff 2013; Breton et al. 2013; Dheer et al. 2015). Differences in microbiota species, diversity and distribution, for example, are extensively described in inflammatory bowel disease (Cucchiara et al. 2009; Ottman et al. 2012). 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 (Konstantynowicz et al. 2012). Elevated oxalates may have deleterious consequences which include mitochondrial damage, generation of ROS, oxidative stress, repression of cellular respiration (TCA cycle), and reduction in antioxidant enzymes and glutathione (Jonassen et al. 2003; Farooq et al. 2014). High oxalate levels contribute to cellular dysregulation and malfunction, which may further translate into clinical manifestations and disease (Veena et al. 2008), such as nephrolithiasis (Bagga et al. 2013) and mental health issues including autism (Konstantynowicz et al. 2012).

A fundamental realization relating to biome alterations has been the recognition that the ability to effectively eliminate toxic compounds requires a healthy, functioning biome (Betts 2011). Accordingly, concerted efforts are being explored to prevent biome damage in the early stages of life (Arrieta et al. 2014), 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 (Mattila et al. 2012; O'Horo et al. 2014). 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 (National Institute of Environmental Health Sciences: Division of Extramural Research and Training Cellular OaSPB 2012; Samsel & Seneff 2013; Breton et al. 2013).

Autonomic nervous system (ANS) dysregulation

The 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 diarrhea, 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 in inhibitory ways. For example, some xenobiotics, such as assorted chemical warfare agents (Ganesan et al. 2010), 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 (CS_2), 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 (Togo & Takahashi 2009).

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 (Togo & Takahashi 2009; Cobb et al. 2012). Exposure to particulate matter, a common event in polluted areas, has also been associated with ANS changes and increased arrhythmogenicity (Folino et al. 2009). 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 (Folino et al. 2009).

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 synthesized 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 (Coghlan et al. 2012). GABAergic malfunction has been associated with epilepsy, cognitive impairment, anxiety, neurodevelopmental disorders, and ASD (Coghlan et al. 2012). 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 (Arakawa et al. 1991; Lasley & Gilbert 2002; Hendriks et al. 2010). 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 (Hendriks et al. 2010).

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 (Stavenes Andersen et al. 2009). 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 (Mariussen & Fonnum 2003; Stavenes Andersen et al. 2009).

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 (Werbach 1997).

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 (Kjellstrom 1992). Cadmium can also contribute to zinc deficiency (Kim et al. 2015). 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 (Moss 2007).

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 (Walker et al. 2012; Boeckxstaens 2015; Xu & Chen 2015; Frenzel & Hermine 2013; Kenna & Brown 2013; Conti & Kempuraj 2016; Latar et al. 2016). Mastocytosis (Latar et al. 2016; Shih et al. 2016) and mast cell activation (Afrin 2016; Regauer 2016) 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 (Schedle et al. 1998; Kempuraj et al. 2010), arsenic (Shim et al. 2016), some pesticides (Yasunaga et al. 2015), phthalates (Nakamura et al. 2002), bisphenol A (O'Brien et al. 2014), as well as some mold and mycotoxin exposures (Urb et al. 2009; Niide et al. 2006).

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.

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 B12
Antibiotics	Vitamin K, L-leucine, Biotin
Atorvastatin	Coenzyme Q10
Beta-adrenergic blocking agents	Coenzyme Q10
Bile acid sequestrants	Calcium, carotenoids, folic acid, vitamins A, D, E, K, zinc
Bisacodyl (Dulcolax, stimulant laxative)	Potassium
Chemotherapy	Magnesium, vitamin B2, taurine, and many other nutrients
Cholestyramine	Carotenoids, fat, folic acid, calcium, iron, magnesium, phosphorus, zinc, vitamin A, vitamin B12, vitamins A, D, E, K
Conjugated oestrogens (Premarin)	Vitamin B6
Corticosteroids	Calcium, DHEA, magnesium, melatonin, potassium, folic acid, vitamin B6, B12, C, D, K, E, selenium, zinc
Digitalis (Digoxin, Lanoxin, Digitoxin)	Magnesium, calcium, sodium, potassium
Diuretics	Magnesium, potassium, zinc, vitamin B1
L-dopa (Levodopa, Dopar, Larodapa)	Vitamin B6, potassium
Edetate calcium disodium (EDTA)	Calcium, zinc
Furosemide (Frusemide, loop diuretic)	Calcium, magnesium, potassium, vitamin B1, Vitamins B6 and C
Heparin	Vitamin D
Histamine H2-antagonists	Iron, zinc, folic acid, vitamin B12
Isoniazid (INH, Laniazid, Rifamate, Rimactane)	Calcium, folic acid, magnesium, vitamins B3, B6, B12, D, E, K
Losartan (Cozaar, angiotensin-II receptor antagonist)	Calcium, chloride, magnesium, potassium, sodium, phosphate
Metformin (Glucophage)	Vitamin B9, B12
Methotrexate	Calcium, vitamin B9
Oral contraceptives	Magnesium, manganese, Zinc, Folic acid, vitamins B1, B2, B3, B6, B12, C
Proton Pump Inhibitors	Beta carotene, vitamin B12, calcium
Simvastatin (Zocor)	Coenzyme Q10, vitamin E, beta carotene
Thiazide diuretics	Magnesium, potassium, sodium, zinc
Ventolin (Albuterol/Salbutamol/Proventil)	Calcium, magnesium, phosphate, potassium

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 (Jandacek et al. 2005).

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 (Knox 2005), reproductive dysfunction (Hauser et al. 2005), endocrine dysregulation (Ashby et al. 1997), immune alteration (Anyanwu et al. 2003), congenital anomalies (Khattak et al. 1999), as well as neurological and psychiatric dysfunction (Genuis 2008). 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 (Genuis 2011; Ross & Sternquist 2012; Jandacek & Genuis 2013; Genuis et al. 2013; Bernhoft 2013).

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 (NHANES 2012; Health Canada 2013; Di Renzo et al. 2015), the ensuing metabolic disruption is not without consequence for individual and global health – a reality that is now ineluctable.

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