Protective Mechanisms and Susceptibility to Xenobiotic Exposure and Load

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D. Noland et al. (eds.), *Integrative and Functional Medical Nutrition Therapy*,
https://doi.org/10.1007/978-3-030-30730-1_13

13.1 Introduction

Human exposure to exogenous toxin sources (xenobiotics) has increased dramatically over the last few decades as a result of industrialization and globalization. This results in exposures that may be greater, more frequent, and qualitatively different, especially with regard to exposure to new-to-nature substances, compared with exposures that have typified the greater part of our species' evolution prior to the Industrial Revolution.

More than 100 million substances (organic and inorganic chemicals) have been added to the Chemical Abstracts Service (CAS) registry system since its inception in 1965. About 75% of those were added in the last decade, exemplifying the exponential increase in registrations [1]. While the number of chemicals manufactured in high volumes and released into the environment represents a minor fraction of these, it is estimated that there are between 100,000 and 200,000 industrial chemicals in common circulation [2]. The toxicology of the vast majority of these isolated chemicals is either unknown or poorly understood. Even less is known about the effects of complex mixtures of compounds to which humans in industrial societies are routinely exposed.

By definition, *xenobiotics* are substances that are foreign to an organism, the term stemming from the Greek word *xenos* meaning foreigner and *bios*, life. In relation to human health, the term xenobiotic is typically used to refer to artificial substances, which did not exist in nature before their synthesis by humans (e.g. polychlorinated biphenyls, dioxins, pesticides). Alternatively, the term may be used to describe other exogenous toxin sources that are present in much higher concentrations than might be expected naturally (e.g. following consumption of cadmium or mercury-contaminated fish) or ones that would not be expected to be found within a human (e.g. bacterial toxins, mycotoxins).

Exposures are typically regarded as being either acute or chronic. In the case of the former, the toxicity usually manifests after a single, major exposure, and symptoms of toxicity in one or more organs (e.g. liver, kidney, brain, nervous system) are usually evident clinically within a short period (<24 h) following exposure. An example of an acute exposure includes an overdose of non-steroidal anti-inflammatory drugs (NSAIDs) associated with attempted suicide. Chronic toxicity, by contrast, is the result of repeated, lower-dose exposures over longer periods of time. Again, using NSAIDs as an example, long-term usage of this category of drugs can result in long-term damage to the liver [3] and gastrointestinal tract [4], especially the small intestine [5].

Exposure to some xenobiotics may lead concurrently to beneficial effects and adverse effects (e.g. pharmaceuticals). Exposure to xenobiotics may also yield no evident adverse or beneficial effect, owing to a low (i.e. sub-acute) exposure concentration or insufficient duration or frequency of exposure. Adverse effects, such as carcinogenicity, may arise from either acute or chronic exposure and may be delayed, taking years or decades to manifest clinically. Other categories of delayed adverse effect include mutagenicity (potential to cause mutations, as measured, for example, by the Ames test) [6], genotoxicity (potential to cause damage to a cell's DNA or RNA), reprotoxicity (potential to cause adverse effects on sexual function and fertility in males and females, developmental toxicity in the offspring, and effects through or via lactation) and teratogenicity (potential to cause birth defects, typically evaluated in laboratory animals).

The Globally Harmonised System of classification and labelling of chemicals (GHS) (revision 6, 2015) identifies 10 categories of health hazard, namely, acute toxicity, skin corrosion/irritation, serious eye damage/eye irritation, respiratory or skin sensitization, germ cell mutagenicity, carcinogenicity, toxic to reproduction (reprotoxicity), specific target organ toxicity/single exposure, specific target organ toxicity/repeated exposure, and aspiration hazard [7].

Organs and body systems that have specific sensitivities to xenobiotics include the liver, kidney, nervous system/brain, mitochondria, endocrine system, immune system, eyes, and skin. Substances that adversely affect one particular system are referred to accordingly, for example, hepatotoxins (liver), nephrotoxins (kidney), neurotoxins (nerves/brain), mitochondrial toxins, endocrine disruptors, immunotoxins, etc.

Xenobiotic exposure in a given individual may exceed the body's innate biotransformation capacities and contribute to a wide range of different pathologies. Some xenobiotics may affect quality of life, increase the risk of cancer, or impact reproductive potential. While the human body has been gifted with a multitude of different mechanisms and pathways to reduce body burdens of xenobiotics, these have evolved to cater for both the types and exposures of xenobiotic substances associated with the majority of our evolutionary history. Mammals such as humans are less likely to be able to adapt quickly to synthetic xenobiotics as compared with natural ones to which humans have been exposed during the majority of our species' evolution. Long generation times coupled with low selection pressure will limit or slow the rate of evolutionary adaptation to xenobiotics. Hence, herbivorous insect 'pests' that are pre-adapted to a multitude of host plant secondary metabolites (phytochemicals) have the capacity to rapidly develop *insecticide resistance*, a process aided by high selection pressure, rapid generational turnover rate, and prior adaptation of an array of detoxification enzymes [8]. Honeybees, by comparison, that have not needed to adapt to a high phytochemical load, have a much lesser array of protein coding genes, thus creating a marked reduction in the diversity of cytochrome P450 enzymes, glutathione-S-transferases (GSTs), and carboxyl/cholinesterases (CCEs) compared with herbivorous insects. This, in turn, likely accounts for the honeybee's extreme sensitivity to insecticides [9].

In human evolutionary terms, the time scale during which most adaptations evolved represents a period of some tens of thousands of years, excluding the most recent 250 years or so since the Industrial Revolution. The past 70 years has seen the rapid development of industries reliant on organic chemistry (e.g. industrial chemicals, food tech-

nology, plastics, agrochemicals, pharmaceuticals, personal hygiene, cosmetics) and biotechnology (e.g. nanomaterials, vaccines) that now represent important sources of xenobiotic exposure of humans. In addition, the growth, intensification and globalization of large-scale industry, continued reliance on fossil fuels as the primary energy source, increased human dependence on technology and the continuing expansion of polluting transportation systems (road, sea, and air) are associated with significantly increased indoor and outdoor pollution burdens compared with those that occurred over the majority of human evolutionary history.

Possible routes of exposure to xenobiotics are shown in ▶ Box 13.1.

Box 13.1 Routes of Exposure to Xenobiotics

Exposure to xenobiotics occurs via one or more of the following routes:

1. Prenatal [10]: Relevant for xenobiotics capable of placental barrier (e.g. tobacco smoke, mercury, lead, SSRI drugs)
2. Oral: Exposure via breast milk, food, water, beverages, drugs, supplements
3. Inhalation: Relating to both outdoor and indoor pollution
4. Dermal: Especially in relation to cosmetics, toiletries, washing water, medications exposed via the skin, eyes, vaginal, and other mucous membranes
5. Intramuscular: Vaccines and their associated adjuvants may represent important xenobiotic exposure that bypasses both the dermal and gastrointestinal barriers.

13.2 Biotransformation

A healthy human body, uncompromised by polymorphisms affecting critical enzymatic biotransformation (detoxification) pathways, is highly adapted to handling a diverse range of xenobiotic substances below dosage or exposure thresholds that might yield adverse effects. In fact, the body is gifted with an array of xenobiotic-sensing receptors, such as the pregnane X receptor (PXR) that has evolved to regulate genes involved in the metabolism and transport of xenobiotics absorbed from food or the environment and protect the body from their harmful effects [11].

The biotransformation process essentially involves two main phases, referred to as phase 1 and phase 2, respectively. In the former, non-polar, lipophilic xenobiotics are most commonly enzymatically converted to polar metabolites via a diverse family of cytochrome P450 enzymes (CYP), especially in the liver, and also in the kidney, lung, brain, adrenal gland, and gut. In some cases, the polar metabolites may be more cytotoxic than the original xenobiotic, for example, the biotransformation of the insecticide DDT to the metabolite DDE [12], or in the activation of polyaromatic hydrocarbons and nitrosamines in the diet to form carcinogens [13].

Other phase 1 enzymes include flavin-containing monooxygenase (FMO), hydrolyses, epoxide hydrolyses, aldehyde dehydrogenase, monoamine oxidases, and xanthine oxidase [14]. In general, these phase 1 metabolites become substrates

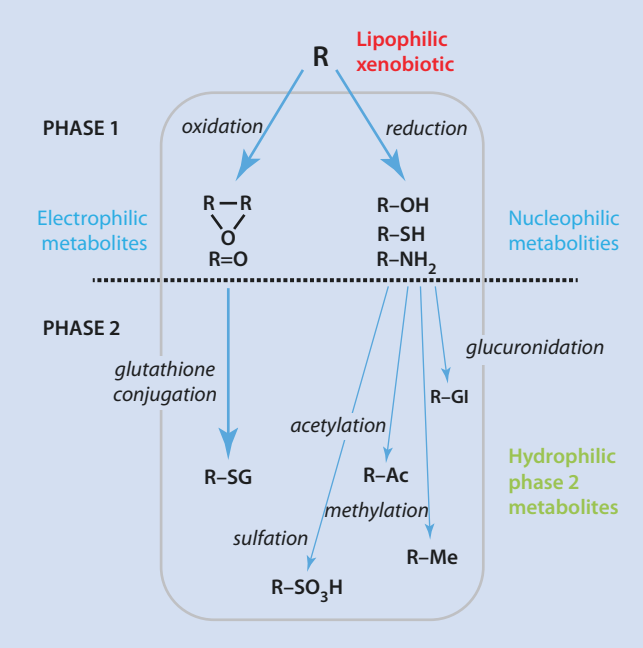

Fig. 13.1 Summary of typical biotransformation of a lipophilic xenobiotic

for phase 2 conjugase enzymes, and following sulfation, amino acid conjugation, glutathione conjugation, glucuronidation, methylation, or acetylation are rendered both less toxic and more water soluble, thereby contributing to urinary or fecal (via the biliary route) excretion (Fig. 13.1) [15]. Chemically modified (more polar) xenobiotics may also be excreted via sweat, as volatile substance by lungs or in human milk [14].

There is increasing recognition of the existence of a complex active transporter (pump) system that is capable of acting on specific xenobiotics (most research having been carried out in relation to pharmaceutical drugs). These are sometimes classified into two discrete, additional biotransformation processes, referred to, respectively, as phase 0 and phase 3 [16, 17].

Both phase 1 and 2 enzymes are highly polymorphic [18]. Accordingly, genetic polymorphisms may contribute to significant inter-individual differences in xenobiotic clearance and responses [19]. A range of other factors also influence inter-individual variations in metabolism of, and response to, xenobiotics, including age, disease status, hormonal changes in the body, ingestion of medications, net exposure to environmental chemicals, and changes in lifestyle, including factors such as cigarette smoking, alcohol consumption, and diet [20, 21].

Given the continued unravelling of the science on biotransformation mechanisms and the growing body of evidence demonstrating the influence of diet and lifestyle on phase 1 and 2 biotransformation, more attention is being placed on dietary and lifestyle modifications that not only reduce the xenobiotic load (i.e. behavioural adaptation to xenobiotics) but also ones that enhance xenobiotic clearance via different and multiple biotransformation pathways.

Dietary composition and individual bioactive constituents can have particularly profound effects on the metabolism of xenobiotics. Animal studies have demonstrated that diets rich in specific saturated and polyunsaturated fats may alter CYP expression, notably of CYP2E1 [22, 23].

Inter-individual responses vary not only according to the potency of the xenobiotic agent(s) and the frequency of cumulative exposure, but also as to the individual's capacity to biotransform and eliminate the agent(s) at a given time. This capacity is dependent on numerous factors, including age, health (including inflammatory) status [24], body size/weight, nutrition, lifestyle, epigenetic background, and polymorphisms affecting biotransformation enzymes.

The clinical phenomenon of *multiple chemical sensitivity* is increasingly well recognized and was usefully defined at a workshop of experts, conducted at the request of the U.S. Environmental Protection Agency (EPA) in 1988, 'as an adverse reaction to ambient doses of toxic chemicals in our air, food, and water at levels which are generally accepted as subtoxic' [25]. The expert workshop concluded that adverse reactions manifest in susceptible individuals depending on a variety of factors, including:

1. The tissue or organ involved
2. The chemical and pharmacologic nature of the toxin
3. The individual susceptibility of the exposed person (genetic makeup, nutritional state, and total load at the time of exposure)
4. The length of time of the exposure
5. The amount and variety of other body stressors (total load) and synergism at the time of reaction
6. The derangement of metabolism that may occur from the initial insults [25]

Intra-individual variation in susceptibility to xenobiotics may also occur temporally, with some patients developing increasing tolerance, or, conversely, increased susceptibility, following continued or repeat exposure to particular xenobiotics.

13.3 Pathophysiology

13.3.1 Mechanisms

Given the huge array of xenobiotics to which humans are now exposed [26] and the general acceptance of their key importance in the pathogenesis of chronic diseases, such as certain types of cancer, it is perhaps surprising that so little, rather than so much, is known about the specific mechanisms by which their effects are mediated. Among the challenges to our improved understanding of the real-world interactions between xenobiotics and humans are the sheer number of xenobiotics to which humans are exposed (and the lack of toxicological knowledge about most of these); the quantitative and qualitative differences in chemical load over time; the challenges facing the study of the effects of exposure to complex mixtures as compared with isolated xenobiotics; [26] the complexity of multigene-environment and epigenetic interactions; the confounding effect of dietary and lifestyle choices; and profound inter-individual variations in susceptibility and tolerance [27].

Dysfunction in homeostatic processes often involve disturbances to the function of interrelated 'super-systems' (e.g. inflammatory, immune, endocrine, neurological) or they may be linked to specific organs or tissues (e.g. liver, kidney, mitochondria, motor neurons).

While there are very large gaps in our knowledge of the mechanisms by which xenobiotics induce adverse effects, three of the most well-researched mechanisms are as follows:

1. *Interference with critical biotransformation steps*. A number of xenobiotics are known to block critical steps in the production of biotransformation enzymes. For example, mercury (e.g. as a contaminant in food) or nitrous oxide (as a gaseous anaesthetic or airborne pollutant) act as potent inhibitors of cobalamin-dependent methionine synthase [28, 29], a critical intermediary in the methionine cycle that is required to synthesize endogenous glutathione, which has the capacity to detoxify both xenobiotics.
2. *Induction of supra-physiological oxidative stress*. Normal metabolic processes, exposure to xenobiotics in our food and environment generate both reactive oxygen species (ROS) and reactive nitrogen species (RNS) [30]. Radical ROS species, characterised by the presence of one or more unpaired electrons, are highly reactive, short-lived molecules, reacting especially with DNA, proteins, and lipids, causing an alteration in their function. While ROS are vital to numerous processes, including signalling cell growth and differentiation, regulating enzyme activity, vasodilation and protecting the host from pathogens and foreign particles, excessive oxidative stress may give rise to DNA, cellular or tissue damage, or to alterations to enzyme function or intracellular signalling pathways. This may, in turn, trigger a wide range of chronic diseases, including heart disease [31] or cancer [32].
3. *Dysregulation of xenobiotic nuclear receptors.* A variety of nuclear receptors, ligand-specific transcription factors, have evolved to sense the presence of toxic metabolites of endogenous metabolism as well as exogenous xenobiotics to which humans are exposed, most notably in the diet. They play a crucial role in biological development, differentiation, metabolic homeostasis, and protection against xenobiotic-induced stresses [33]. Depending on the ligand and the presence of specific cofactors, these nuclear receptors regulate transcription factors that, when functioning properly, control biological functions. However, when expression of these nuclear receptors is dysregulated, they are associated with a wide range of chronic diseases, including asthma, type 2 diabetes, obesity, atherosclerosis, osteoporosis, and cancer [34, 35].

In humans, nuclear receptors can be divided into two main groups according to their ligand-binding specificity [36]:

1. *Orphan receptors*, e.g. constitutive androstane receptor (CAR, NR1I3), pregnane X receptor (PXR, NR1I2), aryl hydrocarbon receptor (AhR), and peroxisome proliferator-activated receptors (PPAR), expressed particularly in the liver and intestines and also in a wide range of other tissues.

   These receptors express a broad range of biotransformation enzymes including CYP1A, CYP1B, CYP2B, CYP3A, CYP2Cs, CYP2A, GSTA1, ALDH1A, MRP3, and MDR1 [32], as well as phase-2 enzymes such as Uridine diphospho-glucuronosyltransferases (UDPGT), glutathione S-transferases (GSTs), and sulfotransferases (SULTs) [37].

   While it has been established that phenobarbital is a major ligand, these receptors have been found to be promiscuous, engaged in 'cross-talk' by stimulating expression of multiple genes, and their function may be promoted (agonist) or repressed (antagonist) by a very broad range of environmental, occupational, and natural products, including many pesticides, pharmaceuticals, dietary chemicals, herbal remedies, and industrial chemicals, typically at micromolar concentrations [36].

   Presently, more than 11,000 ligands have been added to the Orphan Nuclear Receptor Ligand Binding Database (ONRLDB) [► www.onrldb.org], with more than 6500 of these being unique. Orphan receptors for which endogenous ligands are later discovered are referred to as 'adopted orphan' receptors.
2. *Steroid receptors*, e.g. androgen receptor, estrogen receptor (ER), glucocorticoid receptor (GR), and vitamin D receptor (VDR). These receptors are responsive to steroid hormones and exposure to nanomolar concentrations of endocrine-disrupting chemicals (EDCs) such as xenoestrogens which may disrupt normal estrogen signalingsignalling and lead to disease (e.g. estrogen-related cancers) [38].

   Disruption of the function of these receptors and their cross-talk with a broad range of signalling pathways means that xenobiotics affecting steroid receptors may contribute to a daunting range of endocrine-related diseases including metabolic diseases such as cardiovascular, type 2 diabetes and obesity [36], and thyroid diseases [39].

13.3.2 Chronic Diseases Related to Xenobiotic Exposure

Chronic diseases are multifactorial and manifest following highly complex multi-gene/multi-environment interactions, usually over many decades. With limited exceptions (e.g. asbestos- or smoking-related cancers), given the plethora of possible causations, it is often difficult to identify with a high degree of certainty specific causes for particular chronic diseases, given that real-world interactions over multiple decades are likely to give rise to what has been referred to as *symphonic causation* [40].

Given also the vast array of environmental chemicals to which humans are now exposed, it is usually not possible to determine accurately the contribution of environmental chemicals to chronic disease. Notwithstanding this dilemma, exposure to some xenobiotics has been strongly related to specific chronic diseases.

One of the most comprehensive efforts to associate xenobiotic agents with genetic mediators of disease has been through the open-source Comparative Toxicogenomics Database (CTD) [► www.ctdbase.org], an NC State University initiative. The database divides chemicals for which an inferred relationship has been made with human diseases and specific genes into 13 groups and provides an inference score (high score = high inference), with links to the relevant peer-reviewed references. ◘ Table 13.1 provides examples of proven or inferred associations.

The great investment in cancer research over recent decades, the increasing recognition of the importance of environment factors as key triggers in carcinogenesis (as well as in the pathology of other inflammatory and metabolic diseases), along with the emergence of cancer as the leading cause of death in most industrialized, and increasingly in less-industrialized, countries, has stimulated increased interest in establishing scientific consensus over the carcinogenic status of xenobiotics. This role is largely fulfilled by the International Agency for Research on Cancer (IARC), an intergovernmental agency of the World Health Organization (WHO), which publishes comprehensive monographs of the present state of knowledge on carcinogens or potential carcinogens. ◘ Table 13.2 provides a summary of current classifications (including monograph 118) into the five IARC groups.

While the IARC has had a long history of criticism from independent quarters for making 'soft-touch' decisions that avoid negative impacts on the chemical or tobacco industry, it has committed to be more objective [41]. The 2015 decision to include processed meats in Group 1 and the world's top-selling herbicide, glyphosate, in Group 2A, are likely examples of this shift.

While the body of evidence linking a wide range of environmental chemicals to a variety of cancers is indisputable [42], the evidence for an association between environmental chemicals and metabolic diseases like obesity and cancer, as well as processes such as inflammation (refer to ◘ Table 13.1), a key mediator of most, if not all, chronic diseases [43], continues to grow.

Increasing evidence suggests that xenobiotics may interact adversely with the gastro-intestinal (GI) mucosa and microbiome, adversely affecting signalling in the immune, endocrine, and neurological super-system, as well as affecting nutrient assimilation and increasing the risk of a broad range of chronic diseases, including obesity, type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), cardiovascular disease, cancer, and mental diseases [44].

Table 13.1 Chemicals for which associations with human diseases and specific genes have been inferred

CTD chemical category	Top interacting genes	Examples of strongly inferred chemical/human chronic disease relationships [no. genes associated]
Amino acids, peptides, and proteins	CASP3, TNF, GSTP1, IL6, CXCL8, IL1B, MAPK3, ABCB1, MAPK1, HMOX1	Glutathione/prostatic neoplasms [74 genes] Bleomycin/pulmonary fibrosis [35 genes] Cyclosporine/obesity [96]
Biological factors	TNF, IL6, IL1B, NOS2, PTGS2, IFNG, HMOX1, RELA, CXCL8, MAPK3	Lipopolysaccharides/inflammation [79 genes] Mycotoxins/inflammation [15 genes] Aflatoxins/liver neoplasms [2 genes]
Carbohydrates	TNF, NOS2, IL1B, IL6, PTGS2, INS, RELA, IFNG, CASP3, NFKBIA	Lipopolysaccharides/liver cirrhosis [117 genes] Fructose/diabetes mellitus [46 genes] Glucose/carcinoma [59 genes]
Chemical actions and uses	MGEA5, CYP19A1, TNF, IL1B, AR, CASP3, IL6, MAPK1, ACHE, ESR1	Estrogens/carcinoma (hepatocellular) [36 genes] Air pollutants/breast neoplasms [58 genes] Water-pollutant chemicals/breast neoplasms [51 genes] Pesticides/prostatic neoplasms [51 genes] Adjuvants (immunologic)/inflammation [12 genes]
Complex mixtures	TNF, IL6, CXCL8, IL1B, NFE2L2, PTGS2, CYP1A1, HMOX1, NOS2, CAT	Tobacco smoke pollution/stomach neoplasms [102 genes] Smoke/breast neoplasms [101 genes] Particulate matter [lung neoplasms] [79 genes] Chinese herbal drugs/carcinoma (hepatocellular) [55 genes] Vehicle emissions/breast neoplasms [250 genes] Petroleum/prostatic neoplasms [26 genes] Particulate matter/autoimmune diseases [18 genes]
Enzymes and coenzymes	POR, SLC5A6, AKR1B8, CAT, PPARA, CASP3, GAPDH, CYP3A4, NQO1, NQO2	NAD/obesity [8 genes] Thioctic acid/hypertension [41 genes] Leucovorin/heart diseases [2 genes]
Heterocyclic compounds	NOG, AHR, PPARA, CYP1A1, TNF, CASP3, MAPK1, MAPK3, HMOX1, CYP3A4	Tetrachlorodibenzodioxin (TCDD)/liver cirrhosis [763 genes] 2-amino-1-methyl-6-phenylimidazo(4,5-b)pyridine (heterocyclic amine)/carcinoma (multiple) [109+ genes] Nicotine/stomach neoplasms [65 genes]
Hormones, hormone substitutes, and hormone antagonists	ESR1, AR, ESR2, PGR, FSHB, EGF, MAPK1, MAPK3, LHB, TNF	Dihydrotestosterone/prostatic neoplasms [77 genes] Testosterone/breast neoplasms [173 genes] Estradiol/mammary neoplasms [112 genes] Estrogens /carcinoma (hepatocellular) [36 genes]
Inorganic chemicals	APP, CASP3, TNF, HMOX1, CAT, MAPK1, MAPK3, HIF1A, NOG, IL1B	Cadmium/prostatic neoplasms [166 genes] Asbestos/malignant mesothelioma [36 genes] Sodium chloride (dietary)/hypertension [52 genes] Sodium arsenite/ carcinoma (hepatocellular) [147 genes] Arsenic/prostatic neoplasms [168 genes] Hexavalent chromium/lung neoplasms [42 genes]
Lipids	TNF, NOG, IL6, NOS2, IL1B, PTGS2, IFNG, RELA, PPARA, MAPK3	Dietary fats/prostatic neoplasms [222 genes] Arachidonic acid/inflammation [30 genes] Palmitic acid/insulin resistance [18 genes]
Nucleic acids, nucleotides, and nucleosides	CASP3, TP53, TNF, STAR, IL4, IFNA1, CDKN1A, IL6, IL1B, MAPK1	Decitabine (demethylation chemotherapy drug)/carcinoma (hepatocellular) [94 genes] Azathioprine (immunosuppressive drug)/colonic neoplasms [14 genes]
Organic chemicals	NOG, TNF, CASP3, MAPK1, PPARA, MAPK3, CYP1A1, AHR, PTGS2, ACHE	Benzo(a)pyrene/prostatic neoplasms [382 genes] Bisphenol A/prostatic neoplasms [462 genes] Diethylhexyl phthalate/breast neoplasms [112 genes] DDT/carcinoma (hepatocellular) [38 genes] Polychlorinated biphenyls/breast neoplasms [75 genes] Benzene/lung neoplasms [54 genes] Dieldrin Acrylamide/breast neoplasms [35 genes] 1,2,5,6-dibenzanthracene (polyaromatic hydrocarbon)/carcinoma [24 genes] Glyphosate/colonic neoplasms [13 genes]

Table 13.1 (continued)

CTD chemical category	Top interacting genes	Examples of strongly inferred chemical/human chronic disease relationships [no. genes associated]
Polycyclic compounds	AHR, ESR1, CYP1A1, TNF, CASP3, AR, HMOX1, MAPK1, MAPK3, ESR2	Benzo(a)pyrene/prostatic neoplasms [382 genes] Polycyclic hydrocarbons (aromatic)/breast neoplasms [28 genes] Simvastatin/liver cirrhosis [31 genes] Naphthalene/lung neoplasms [34 genes]

Based on data from: Comparative Toxicogenomics Database [CTD] [► www.ctdbase.org]

Table 13.2 International Agency for Research on Cancer (IARC) categorisation of carcinogens and examples

IARC category	Scientific basis of IARC classification	Number of entries (2017)	Examples
Group 1	Carcinogenic to humans	120	Alcoholic beverages, aflatoxins, aristolochic acid, arsenic, asbestos, benzene, benz(a)anthracene, cadmium, benzo(a)pyrene, coal, coal tar, chromium (VI) compounds, diesel exhaust, dioxin, ethanol in alcoholic beverages, lindane, Epstein-Barr virus, Estrogen-progestogen menopausal therapy (combined), Estrogen-progestogen oral contraceptives (combined), ethylene oxide, formaldehyde, *Helicobacter pylori* infection, Hepatitis B and C virus (chronic infection), human papillomavirus (HPV) types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, ionizing radiation, leather dust, untreated mineral oils, naphthylamine, nickel compounds, paints (occupational exposure of painters), polychlorinated biphenyls, outdoor air pollution, processed meat (consumption of), radionuclides, various forms of radium and their decay products, rubber manufacturing industry, salted fish (Chinese style), shale oils, crystalline silica dust, solar radiation, soot, Tamoxifen, tobacco (smoking, second-hand smoke, smokeless, chewing), trichloroethylene, ultraviolet-emitting tanning devices, vinyl chloride, wood dust, X- and Gamma-radiation
Group 2A	Probably carcinogenic to humans	81	Acrylamide, anabolic steroids, adriamycin, wood (and other biomass) fuels, bitumens, Captafol, chlorinated toluenes, chlorozotocin, Cisplatin, creosotes, cyclopentalpyrene, dibenzacridine, dibenzopyrene, dimethylhydrazene, dimethyl sulphate, ethyl carbamate (urethane), ethylene dibromide, emissions from high temperature frying, occupational exposure as hairdresser or barber, glyphosate, inorganic lead compounds, infection by *Plasmodium falciparum* (that causes malaria), mate (hot), Merkel cell polyomavirus, 5-methoxypsoralen, methyl methanesulfonate, N-methyl-N′-nitro-N-nitrosoguanidine (MNNG), ingested nitrates or nitrites (under conditions that result in endogenous nitrosation), nitrogen mustard, 1-nitropyrene, N-nitrosodimethylamine, N-nitrodimethylamine, 2-nitrotoluene, application of non-arsenical insecticides (occupational exposure), petroleum refining, polychlorinated biphenyls (PCBs), red meat (consumption of), shift work involving disruption of circadian rhythms, styrene-7-8-oxide, tetrachloroethylene (perchloroethylene), 1,2,3-trichloropropane, vinyl bromide, vinyl fluoride
Group 2B	Possibly carcinogenic to humans	294	Aflatoxin M1, acetaldehyde, acetamide, para-aminoazobenzene, anthraquinone, benzofuran, benzophenone, benzyl violet 4B, bitumens, occupational exposure to straight-run bitumens and their emissions during road paving, caffeic acid, carbon black, carbon tetrachloride, chloroform, cobalt and cobalt compounds, cobalt metal without tungsten carbide, coconut oil diethanolamine condensate, para-dichlorobenzene, diethanolamine, ethylbenzene, gasoline, human immunodeficiency virus type 2 (infection with), human papillomavirus types 26, 53, 66, 67, 70, 73, 82, lead, magnetic fields (extremely low-frequency), methylmercury compounds, metronidazole, mitoxantrone, naphthalene, nickel (metallic and alloys), nitrobenzene, ochratoxin A, pickled vegetables (traditional in Asia), phenobarbital, styrene, talc-based body powder (perineal use)

(continued)

Table 13.2 (continued)

IARC category	Scientific basis of IARC classification	Number of entries (2017)	Examples
Group 3	Not classifiable as to carcinogenicity in humans	505	Aciclovir, actinomycin D, amaranth, para-aminobenzoic acid, ampicillin, anaesthetics (volatile), arsenobetaine and other organic arsenic compounds that are not metabolized in humans, atrazine, benzoyl peroxide, bisphenol A, diglycidyl ether (Araldite), bisulfites, caffeine, carrageenan (native), chlorinated drinking water, chloroquine, cholesterol, chromium (metallic), coal dust, coumarin, crude oil, cyclamates (sodium cyclamate), diazepam, electric fields (extremely low-frequency), electric fields (static), ethylene, fluorides (inorganic, used in drinking-water), haematite, human papillomavirus genus beta (except types 5 and 8) and genus gamma, lead compounds, organic (NB: Organic lead compounds are metabolized at least in part, to ionic lead both in humans and animals. To the extent that ionic lead, generated from organic lead, is present in the body, it will be expected to exert the toxicities associated with inorganic lead), magnetic fields (static), mineral oils (highly refined), acetaminophen (paracetamol), polyethylene, polypropylene, polystyrene, saccharin and its salts, tea, temazepam, vitamin K substances
Group 4	Probably not carcinogenic to humans	1	Caprolactam

Emerging evidence suggests that xenobiotics may cause significant alteration to the microbiota in the human gut. Antibiotics and other oral pharmaceuticals may create significant short- or long-term changes in GI microbiome stability as well as changes to the relative abundance of particular bacterial taxa. Older patients on long-term prescriptions and polypharmacy may suffer reduced microbiota stability and diversity [45]. A study on the effect of the antibiotic cephalosporin on wild gorillas showed that the drug had a statistically significant tendency to increase *Firmicutes* (Gram positive) and decrease *Bacteroidetes* (Gram negative) colony numbers and species diversity, [46] a pattern that is associated with obesity in humans [47].

Further evidence implicates certain groups of pesticides, persistent organic pollutants (e.g. polychlorinated biphenyls), heavy metals (e.g. cadmium, mercury), food additives, and nanomaterials in further disturbances to the GI microbiota [48].

Xenobiotics, most notably excitotoxins and neurotoxins capable of passing the blood–brain barrier such as those transported by P-glycoprotein, are increasingly implicated in neurological diseases such as Parkinson's disease [49, 50], especially among those who are genetically more susceptible (e.g. organophosphate insecticide-exposed individuals homozygous for the paraoxonase 1 (PON1–55) gene) [51].

Other organs, tissues, and organelles that may be particularly vulnerable to xenobiotics are those directly involved in biotransformation (liver, kidney) [52], excretion (colon, bladder, urethra) [53], and energy production (mitochondria) [54].

13.4 Clinical Considerations

Where xenobiotics are thought to have been a trigger or mediator of a particular disease or condition, an integrative and functional medicine approach necessitates three main areas of investigation prior to the development of a treatment plan:

13.4.1 Assessment of Xenobiotic Exposure, Historically and Presently

This assessment, likely based on patient interview, should take into account known prenatal, childhood, occupational, and other lifetime exposures.

Xenobiotics may be categorized according to the CTD (Table 13.1); given the extreme sensitivity to xenoestrogens, consideration should be given to even very low levels of exposure to xenobiotic hormones or hormone analogues that act as endocrine disrupting chemicals (EDCs) even at nanomolar concentrations, close to the limit of analytical detection.

All five routes of potential exposure (▶ Box 13.1) should be considered, taking into account indoor pollutants (e.g. flame retardants, mycotoxins from moulds), xenobiotics in foods (e.g. preserved meats, polyaromatic hydrocarbons/heterocyclic amines on charred/high temperature cooked foods, food additives, sugar, pesticide contamination), outdoor pollutants, chlorinated/fluoridated drinking water, cosmetics, toiletries, etc.

Risk is determined by both the exposure (including dose and frequency) and an individual's susceptibility, the latter being heavily predicated genetically (Table 13.3).

Table 13.3 Important single nucleotide polymorphisms (SNPs) affecting biotransformation of xenobiotics

Phase	Gene	Gene variant	Risk allele	Example of impact	Reference
Phase 1	CYP1A1*1 (M1)	Msp1T>C	C	Metabolic of estrogens and polyaromatic hydrocarbons into carcinogenic reactive metabolites	Moorthy et al. (2015) [55], Sharma et al. (2014) [56]
	CYP1A1*2 (M2)	Ile462ValA>G	G		
	CYP1A2*1C	3858G>A	A	Metabolic activation of heterocyclic amines (HCAs) and aromatic amines (AAs) (e.g. in high temperature cooked meats)	Wang et al. (2012) [57]
	CYP1A2*1F	164A>C	C	CC (homozygote) individuals are 'slow' metabolizers of caffeine	Cornelis et al. (2006) [58]
	CYP2E1	96-bp insertion	N/a	Bioactivation of N-nitroso compounds derived from processed meats containing nitrite preservatives	Jiang et al. (2013) [59], Cross and Sinha (2014) [60]
Phase 2	COMT	Val158M	A	Slow COMT expression may lead to reduced methylation and increased DNA damage	Tahara et al. (2009) [61]
	MTFHR	C677T	T	Homozygote (and to a lesser extent heterozygote) individuals of each polymorphism have impaired methylation, increased risk of neurotransmitter disturbances and cardiovascular disease, and are slow (~70% reduced) metabolizers of folic acid to bioactive 5'-methyl-tetrahydrofolate	Stover (2011) [62], Alizadeh et al. (2016) [63]
	MTHFR	A1298C	T		
	N-acetyltransferase (NAT)2	Multiple, incl. 590A, 341C, 481T, 803G and 282T	Various	Holders of non-wild type alleles may have various combinations of alleles making them slow acetylators, affecting the metabolism of many drugs	Sabbagh et al. (2011) [64]
	Glutathione S-transferase (GST)M1	Deletion	Null	Deletions of these members of the GST gene (mu and theta 1 positions) superfamily are associated with reduced glutathione conjugation and elevated risk of some cancers	Bolt and Their (2006) [65]
	GSTT1	Deletion	Null		
	Aldehyde dehydrogenase (ALDH2)	rs671 G>A	A	Significantly reduced capacity to convert aldehydes (including from alcohol consumption) to acetate	Way et al. (2017) [66]
	PON1–55	55 L>M	M	MM homozygotes are more susceptible to adverse effects following exposure to organophosphate insecticides; associations with increased risk of Parkinson's disease	O'Leary et al. (2005) [67], Manthripragada et al. (2010) [68]
Phase 1/ Phase 2	SULT2B1	Multiple, including SULT2B1b and SULT2B1a	Various	Key member of the steroid metabolizing sulfotransferase (SULT) gene superfamily; imbalanced metabolism of hydroxysterois hormones and cholesterol	Ji et al. (2007) [69]

In some cases, it may be necessary to determine the presence of specific chemicals using relevant tests, e.g. lipid-soluble chemicals following fat biopsy, water-soluble chemicals via urine or sweat, or neurologically active pesticides using acetylcholinesterase assay.

13.4.2 Assessment of Genetic Susceptibility

An increasing array of genetic tests is commercially available to evaluate specific single nucleotide polymorphisms (SNPs) that increase (or decrease) susceptibility to xenobiotic agents (Table 13.3).

Special consideration should be given to individuals expressing multiple high-impact polymorphisms relating to compromised biotransformation.

13.4.3 Assessment of Diet and Lifestyle

Of key importance are elements of diet and lifestyle that affect exposure to, or enhance, biotransformation of xenobiotics.

Diets including regular consumption of highly processed or ready-made foods, high-temperature cooked foods, and ones low in a diversity of vegetables and fruit generally contain larger amounts of synthetic additives, contaminants or other xenobiotic compounds as well as fewer disease protective compounds. Food and lifestyle diaries are a useful means of gaining information about a patient's habits and potential exposures.

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13.5 Clinical Strategies

Key strategies may be divided into those that reduce total xenobiotic load.

13.5.1 Reducing or Avoiding Exposure to Xenobiotics

The most important way of modifying risk to environmental toxins is to avoid, or at least reduce, exposure to them. The following section draws on strategies proposed by renowned functional medicine doctor, Mark Hyman, MD [70].

Reduction or avoidance strategies include:

- Avoid processed foods; consume whole foods, home-prepared for freshness and to avoid nutrient loss where possible
- Consume organically certified or guaranteed pesticide-free produce. This is especially important when consuming fatty foods (e.g. dairy produce, vegetable oils, fatty meats) that tend to accumulate pesticides, veterinary drugs, and POPs
- Reduce or eliminate personal care products that contain harmful ingredients (e.g. phthalates, parabens, PEGs, propylene glycol)
- Eliminate or avoid excess exposure to petrochemicals, agrochemicals, and other sources of environmental toxin, for example, garden chemicals, dry cleaning, car exhaust, second-hand smoke
- Reduce or eliminate the use of toxic household cleaners (use low toxicity, environmentally friendly versions, wear gloves to avoid skin contact)
- Avoid unfiltered, municipal tap water. A reverse osmosis or distillation system are the only two systems that remove xenoestrogens, although it is advised to re-mineralize water (to at least pH 7.5) with a suitable mineral source prior to drinking
- HEPA/ULPA filters and ionizers can be helpful in reducing dust, moulds, volatile organic compounds, and other sources of indoor air pollution
- Avoid high-temperature cooking, such as frying and deep frying
- Avoid using PTFE-coated non-stick-treated pans (that may release fluorine gas during high-temperature cooking)
- Do not drink water or drinks from plastic bottles, unless they are guaranteed BPA-free (use glass bottles)
- Avoid storing food in plastic containers, or covering food in plastic wrapping, especially where food contact occurs, unless it is guaranteed to be phthalate-free (use glass or earthenware for food storage)
- Clean and monitor heating systems for release of carbon monoxide
- Include houseplants throughout house (including bedrooms) to help filter the air and increase oxygen concentration
- Air dry-cleaned clothes in well-ventilated space before wearing or storing
- Use solvent-free (water-based) paints if decorating interior spaces
- Avoid inhaling heavy traffic fumes, especially when exercising heavily (e.g. running, cycling). A respirator containing both particulate and carbon filters will reduce the level of harmful exposure, but filters should be changed regularly
- Understand all sources of possible workplace exposure and take action to avoid or minimise. In some cases, it may be helpful to engage the relevant trade union for assistance
- Use a carbon filter on baths or showers (and replace regularly according to manufacturer specifications) or reduce their duration
- Avoid chlorinated swimming pools; preferably, swim in sea water or other natural, open water or use seawater or ozone-treated pools
- Prospective mothers should ensure they have minimized exposure to environmental toxins 6–12 months before planning to get pregnant and should minimise exposure to xenobiotics throughout breastfeeding
- Avoid taking antacids, paracetamol, or other common over-the-counter medications and seek support for natural/non-drug alternatives
- Remove allergens and dust in living areas as much as possible

- Minimize exposure to electromagnetic radiation (EMR) from cellular or cordless phones by ensuring time spent with handset close to head or body is kept to a minimum. Do not carry phones in pockets or close to the body unless turned off. Do not sleep with phone near bedside if left on. Use 'air tubes' or speakers to reduce proximity of phone to head/body when talking. Use radiation protection cases or sleeves on mobile devices
- If working on computer, ensure screens and main computer are at least 30 cm from body. Use separate wired keyboard and low-radiation screen if laptop is main computer
- Do not use cordless telephones as most base stations emit EMR equivalent to transmission mast 250 m from house. Use corded phones for landlines
- Avoid excessive time (more than 1–2 h/day) watching television or using screens and sit more than 3 m away from television when watching
- Avoid use of microwave ovens
- Avoid excessive exposure to sun (avoid burning)
- Avoid any exposure to X-rays other than those regarded medically essential
- Reduce heavy metal exposure (predatory and river fish, some municipal drinking waters, lead paint, thimerosal-containing products, etc.)

13.5.2 Supporting the Body's Detoxification Capacity

There is a large body of research, as well as decades of clinical experience, supporting nutritional approaches to enhancing biotransformation (detoxification) processes in the body [71, 72].

13.5.2.1 Improve Elimination of Toxins

- Try to ensure 1–2 bowel movements a day
- Drink 6–8 glasses of clean drinking water a day
- Sweat regularly (use exercise, steam baths, and/or saunas to encourage sweating)
- Regular physical activity and exercise, yoga, or lymphatic massage can improve lymph flow and assist elimination of toxic metabolites
- Consume adequate soluble and insoluble fibre: approx. 30g/day
- Consume legumes (generally cooked to reduce/eliminate lectins), whole grains (preferably gluten-free), vegetables, fruits, nuts, and seeds
- Consume fermented foods as natural probiotic sources

13.5.2.2 Foods that Support Biotransformation

- Cruciferous vegetables (cabbage, broccoli, collards, kale, Brussels sprouts) containing indole-3-carbinol, sulforaphane, etc., at least 1–2 cups daily
- Garlic cloves (several daily) or garlic (preferably kyolic aged) supplement
- Decaffeinated green tea; preferably morning
- Freshly made vegetable juices, e.g. kale, celery, cilantro, beets, parsley, ginger, and carrot (the latter should be limited because of its high sugar content)
- Herbal detoxification teas, e.g. burdock root, dandelion root, ginger root, liquorice root, sarsaparilla root, cardamom seed, cinnamon (not cassia) bark, etc.
- High-quality, sulfur-containing proteins; eggs, plant protein (not soya) isolates, as well as garlic and onions
- Citrus peels, caraway and dill oil (limonene sources)
- Bioflavonoid/polyphenol-rich berries, grapes, citrus, and other fruits
- Dandelion greens may help in liver detoxification, improve the flow of bile and increase urine flow
- Celery may increase urine flow
- Fresh cilantro may help eliminate 'heavy metals'
- Rosemary, as fresh herb or extract, promotes expression of biotransformation enzyme genes, chelates heavy metals, antioxidant, anti-inflammatory
- Turmeric/curcuminoids (in fresh and dried turmeric and curry powders): exhibit multi-target functions including detoxification, antioxidant, and anti-inflammatory effects
- Chlorophyll in dark green leafy vegetables, wheat grass, etc.

13.5.2.3 Dietary/Food Supplements that May Support Enhanced Biotransformation

- Full-spectrum, high-quality multivitamin and mineral formula including bioavailable nutrient forms
- Buffered vitamin C (with mineral ascorbates): 1000–4000 mg a day in divided doses (to avoid loose stools) in powder, capsule, or tablet forms during periods of increased detoxification. If dosage causes loose stools, lower dose
- Milk thistle (*Silybum marianum*): 200–600 mg silymarin/day
- Rosemary (*Rosmarinus officinalis*) extract: 200–500 mg dry extract/day (standardized to 6–10% rosmarinic acid)
- Turmeric curcuminoids with bioavailability enhancer (e.g. turmeric essential oils, cyclodextrin, piperine): 200–600 mg curcuminoids/day, in divided doses
- Astaxanthin (from *Haematococcus pluvialis*): 5–20 mg/day
- Vitamin B6 (as pyridoxal 5′-phosphate): 10–25 mg/day
- Vitamin B12 (as methylcobalamin): 500–10,000 µg/day
- Folate as (6S)-5-methyltetrahydrofolate (glucosamine salt), calcium methylfolate, or food-form folates [73]: 1500 µg/day
- Omega-3 fatty acids (as EPA and DHA): 2000–5000 mg/day
- Liposomal glutathione: 400–800 mg/day

Additional supplements (for use under medical supervision):

- N-acetylcysteine: 500–1000 mg a day
- Amino acids: taurine 500 mg twice/day, glycine 500 mg twice/day
- Alpha-lipoic acid: 100–600 mg a day
- L-carnitine: 1000–2000 mg a day in divided doses
- Bioflavonoids (citrus, pine bark, grape seed, green tea): 50 mg/day

13.6 Conclusions

There is growing evidence that xenobiotics are playing an increasing role in a wide variety of chronic diseases and multi-morbidities that present the primary burdens on healthcare system [74]. The specific manifestation of disease in a given individual is dependent on extraordinarily complex and generally poorly understood gene-environment interactions, mediated by disrupted nuclear transcription factor trafficking and signalling pathways.

The huge, variable, and unpredictable array of xenobiotics to which individuals are exposed presently, coupled with the genetic and epigenetic variability, make it almost impossible to assess the net effect of xenobiotic load on an individual. This dilemma is compounded further by the absence of adequate toxicological and toxicogenomic data on environmental chemicals, acting both singly or, even more relevant to real-world situations, as mixtures.

Toxicogenomics offers a new lens through which to understand more about the effects of xenobiotic exposure mediated by effects on specific genes and signalling pathways. The clinical practice of integrative and functional medicine is unique in its emphasis on trying to establish causes, triggers, and mediators of chronic disease, often much earlier in the disease cycle than with conventional medical approaches.

Rapidly emerging omics sciences, including nutrigenomics and metabolomics, as well as cost-effective testing of SNPs for gene variants associated with compromised biotransformation, are further able to assist clinicians in their development of personalised protocols for their patients.

Despite these complexities, a number of robust strategies apply to most, if not all, cases: every effort should be made to help patients minimise total xenobiotic exposure and body load, while dietary and lifestyle patterns that promote effective biotransformation and elimination of metabolites should be strongly encouraged.

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