

Environmental Xenobiotics and Their Adverse Health Impacts-A General Review

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Abstract Environmental xenobiotics are any chemicals of synthetic origin which are not normally expected to present in an organism. There are several environmental xenobiotics that impose adverse impacts both on ecology and human beings. Pesticides, toxic heavy metals, polychlorinated biphenyls and persistent organic pollutants are environmental xenobiotics for which there are ample scientific evidences showing the obnoxious health impacts that these chemicals are imposing on humans. Neurotoxicity, immunotoxicity, nephrotoxicity, hepatotoxicity and cancer are the most frequently mentioned among the numerous health problems associated with environmental xenobiotics. However, their potential toxicities and possible routes of exposure to them are less known by general public. As a result, in this paper an attempt of critically reviewing existing literatures was made so as to support upcoming future studies on the health impacts of xenobiotics so that the results of such study can address the problem on the ground. Consequently, this paper briefly addresses several specific xenobiotic chemicals; routes of exposure and chronic effects of exposure to them.

Keywords: *environmental xenobiotic, health impact, pesticide, toxic heavy metal and persistent organic pollutants*

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1. Introduction

A xenobiotic is defined as a chemical which is found in an organism but which is not normally produced or expected to be present in it [1]. A xenobiotic is a compound that is foreign to a living organism [2]. Xenobiotics are biologically active synthetic chemicals many of which compromise human health [3]. Environmental xenobiotics are substances which did not exist in nature before their synthesis by humans [1]. Experimental, epidemiological and other evidences suggest that such toxic environmental chemicals can lead to a serious adverse health effects.

The immune system is the most vulnerable to detrimental effects of xenobiotics. Immunotoxicity can result in reduced resistance towards infection, generation of tumors that can escape immune surveillance [2,4]. According to Banerjee and co-workers, xenobiotics are immunotoxic to human as they adversely affect humans' immune system. The high lipophilicity and persistence of many of xenobiotics greatly enhances their biomagnification, thereby posing potential health hazards on predators at higher trophic levels [5]. Immunotoxic xenobiotics have the capacity to suppress the body's defenses against pathogenic microorganisms. Many reports in the literature describe the immunotoxic effects of xenobiotics recognizing that the immune system as a whole can be the target for xenobiotic induced toxicity [1].

Liver plays a central role in detoxification and is thus chronically exposed to xenobiotics and their toxic

derivatives [6]. The liver is an important target organ for the toxicity of xenobiotics due to its connection with the gastrointestinal tract, its singularity, complexity of its anatomical structure and metabolic functions [7]. Thus, xenobiotics are suspected of hepatotoxicity [8].

Nervous system is also the target organ of many toxic xenobiotics [9,10,11]. Neurotoxicity occurs when the exposure to neurotoxins induce adverse effects in the central nervous system, peripheral nerves or sensory organs. A chemical is considered to be neurotoxic if it is capable of damaging the nervous system or brain usually by killing neurons or cells which transmit and process signals [12].

Neurotoxicities may be expressed as neuropathologic or altered neurochemical, electrophysiological or behavioral functions [9]. Neurotoxicity is generally manifested as multiple syndromes and effects depending on the nature, level and duration of the exposure to xenobiotics [13].

Toxic heavy metals, polychlorinated, biphenyls and persistent organic pollutant are environmental xenobiotics known for their neurotoxic nature [11,14,15,16]. The adverse effects of neurotoxicity are among the most feared ill health in humans because they adversely affect the quality of life, and have broad health, social and economic implications [9].

Xenobiotics are capable of disrupting mitochondrial function and cause free oxygen and free nitrogen radicals formation. Mitochondrial dysfunction is partly responsible for pathophysiology of age-related chronic diseases such as metabolic syndrome, diabetes, coronary artery disease, acute coronary syndrome, stroke, Alzheimer's disease, Parkinson's, depression and cancer [17].

Some xenobiotics are genotoxic [5]. Genotoxic compounds are those that act directly or indirectly on the DNA or clastogenic event. The genotoxic potential is a primary risk factor for chronic or long-term effects such as reproductive effects and toxicity [15]. Some undisputed lessons from the past demonstrate how xenobiotics in the environment may have profound impact on male reproductive health. The Danish 1992 report on a decline in sperm count have fuelled speculations that the environmental impact may be substantial because only changing environmental factors can explain dramatic changes in health outcomes across short time period [18].

All toxic heavy metals including Pb, Cd, Hg, As and Pd are potentially known as nephrotoxics [14,19,20]. Nephrotoxicity describes all acute or chronic disorders or malfunctions of the structural integrity or the excretory, endocrine, and metabolic function of the kidney which are caused by these exogenous chemical substances [21].

2. Classes of Chemicals that Fall Under Domain of Xenobiotics

Environmental xenobiotics include products of industry such as pesticides, heavy metals, polychlorinated biphenyls, persistent organic pollutant, synthetic drugs, fertilizers, plastics, dyes etc [1,22]. According to Bulucea and co-authors natural xenobiotics like animal poisons and toxins, and toxic products from plant are also xenobiotics to human. The aforementioned first four classes of xenobiotics will be further considered.

2.1. Xenobiotic Pesticides

2.1.1. Pesticide Definition and Classification

A pesticide is a substance intended to prevent, destroy, repel or control any animal pest or disease caused by pests as well as unwanted weeds [23]. It is a generic term that covers a wide spectrum of biologically active compounds including herbicides, fungicides, rodenticides, molluscides, fumigants and insecticides [7,11]. The United States Environmental Protection Agency definition of a pesticide is any substance or mixture of substances intended for preventing, destroying, repelling or mitigating any pest. The term pesticide applies to insecticides, herbicides, fungicides, and various other substances used to control pests [24]. They are designed to impede and prevent the development of living organism or to interfere with their ability to reproduce or to kill them outright [25]. Organochlorines, organophosphates, carbamates, and pyrethroid fall under insecticide class; arsenic trioxide, barium carbonate, anticoagulants etc. are included under category of rodenticides; paraquat, diquat, 2, 4-dichlorophenoxyacetic acid etc. are under the domain of herbicides; and ethylene dibromide, methyl bromide etc. are in the sphere of fumigants [16,26].

2.1.2. Exposure Routes to Pesticides

Dietary and occupational exposures are common routes to become in toxic contact with pesticides. Occupational exposure to pesticides is mainly associated with agricultural work; pesticide manufacturing and formulating employees,

highway and railway workers as well as green house, forestry and nursery workers may have a substantial risk of being exposed to neurotoxic pesticides [12]. Although the most susceptible to adverse effects of pesticides are those exposed to them in occupational arena, dietary exposure is also the basic means of exposure of general public to obnoxious health impacts of pesticides [18,27]. WHO [27] report showed almost all fruits and vegetables collected from Karachi markets in Pakistan found to contain the most obnoxious organochlorine pesticide residues like Heptachlor, BHC and DDT at levels dangerous for human health. Exposure to these pesticides can lead to several health problems as they are inhibitors of enzymes and disturb the normal biochemical reactions necessary for metabolism [28].

2.1.3. Toxicities of Pesticides

Pesticides are among the most extensively used chemicals in the world today and they are also among the most hazardous compounds to the humans [28]. Pesticides are toxic by their design and they are also potentially hazardous to human, animals, other organisms as well as the environment [29]. Pesticide causes several different toxicities to human and other animals. Some pesticides are neurotoxic, some are cytotoxic, some are nephrotoxic, some are hepatotoxic, some are immunotoxic, and some are genotoxic [28,30]. There are still some pesticides which show two or more types of toxicities. They have also been associated with long-term carcinogenicity, mutagenicity and hormonal effects [15]. Pesticide exposure before or during pregnancy has been associated with increased risk of infertility, perinatal death, spontaneous abortion, premature birth, fetal growth retardation, congenital malformations and early childhood cancer [29]. The toxic effect of pesticides is not necessarily a result of direct application; some pesticides accumulate into the food to a toxic level and affect the public health [31]. More than 30 years ago it was almost concomitantly reported from the United States and Israel that the nematocide dibromochloropropane causes severely reduced sperm counts and even sterility in workers manufacturing or applying this pesticide [18]. Most adverse health effects by genotoxic agents are the result of genetic damage which most likely to arises from cell division abnormalities [32]. Increased incidence of leukemia and bladder cancer in farmers has also been observed following genotoxic effects of some pesticides. Agrochemicals are able to induce changes in the genetic material of somatic and germinal tissues which are considered mutagenic that contributes to the appearance of congenital malformations and cancer etiology [15]. Pesticides are neurotoxics as they are among the chemicals which may induce polyneuropathy and peripheral neuropathy. Polyneuropathy and peripheral neuropathy are diseases of the peripheral nervous system which affects motor, sensory and autonomic fibers. This may lead to difficulties in walking or in the fine coordination of hands and fingers [12]. A substantial body of animal research and ecologic study has implicated a link between pesticide exposure and impaired neurodevelopment as well as autism in children. Recently, few studies have examined the neurobehavioral consequences in children resulting from chronic, low-level exposure to common pesticides [11]. Pesticides such as herbicides, fumigants, insecticides and

fungicides are human neurotoxicant. Certain organophosphates have caused damage to the afferent fibers of peripheral and central nerves through inhibition of "neuropathy target esterase". This delayed syndrome has been termed organophosphate-induced delayed neuropathy and is manifested chiefly by weakness or paralysis and paresthesias of the extremities [33]. Many pesticides are also associated with kidney disease mediated either by acute tubular necrosis or specific kidney lesions. Such pesticides can cause hemolysis and rhabdomyolysis with subsequent acute nephrotoxicity [14].

Experimental studies on human cell cultures and laboratory animals have provided strong evidence that many pesticides are immunotoxic. Pesticides can target both humoral and cellular components of immune system and these changes correlate closely with alternated host resistance to the pathogens [2]. Furthermore, *In vitro* and animal studies showed that many pesticides have endocrine-disrupting properties [33].

2.1.4. Mechanism of Toxicity of Pesticide

Pesticides have been shown to induce the production of reactive oxygen which ultimately leads to oxidative stress. Researchers have shown that oxidative stress in living cells is caused by the imbalance between the production of free radicals and the generation of antioxidants to detoxify the reactive intermediates or to repair the resulting damage [34]. Pesticide-induced oxidative stress has been considered as a possible mechanism of toxicity. The pesticides are known to increase the rate of lipid peroxidation by altering the activity of both the enzymatic and the levels of non-enzymatic antioxidative reserves of the cell and cause oxidative stress [16].

2.1.5. Organochlorine Pesticides

They are organochlorine compounds that share several properties such as stability against decomposition or degradation by biochemical processes; very low solubility in water and lipophilicity) [35]. Among the major groups of pesticides, organochlorines that consist of DDT, BHC, chlordane, heptachlor, aldrin, dieldrin, endrin, endosulfan etc are the most dangerous due to their persistence and lipophilic nature. These properties allow them to accumulate and bioconcentrate in milk, meat, fish and any food items containing fat [2,36]. In humans organochlorine pesticides or their metabolites act primarily at the level of central nervous system altering the electrophysiological properties and enzymatic neuronal membranes causing alterations in the kinetics of the flow of Na^+ and K^+ through the membrane of the nerve cell, resulting in the spread of multiple action potentials for each stimulus causing symptoms such as seizures and acute poisoning or death from respiratory arrest [15].

2.1.5.1. Adverse Health Impacts of DDT

Reproductive dysfunction, neurotoxicity and potentiality for cancer are often mentioned health impacts of this pesticide [11,22,37]. There is growing evidence that exposure to nanogram levels of DDT may disrupt normal metabolism of sex hormones in fish, birds and mammals. This in turn, may lead to reproductive dysfunction such as reduction in fertility, hatch rate, alternation of sex

behavior and viability of offspring [5]. The insecticide DDT imitates estrogens in animals in addition to causing preterm birth and early weaning, and possible disruption in semen quality, menstruation, gestational length and duration of lactation in humans [22,38].

DDT is known to cause excitation of the central nervous system and can lead to tremors, hyperexcitability and convulsions. DDT's effect on the central nervous system is likely through interrupting the movement of ions through the neuronal membranes which leads to the inappropriate release of neurotransmitters [11].

DDT is potentially human carcinogen. Under circumstances of heavy, prolonged occupational exposure to technical-grade DDT has a potential to cause pancreatic cancer [37]. The toxicity of exposure to DDT is exacerbated by dichlorodiphenyl trichloroethylene (DDE) which is its major metabolite [38]. A potential effect of DDE in humans is the risk of breast cancer, since it is a xenoestrogen or described as an endocrine disruptor with estrogen-like effects. Epidemiological research has indicated that both DDT and DDE are carcinogenic in animals [37].

Experimental studies on animals particularly rat also showed that DDT has hepatotoxicity. Increased liver weights, hypertrophy, hyperplasia, cell necrosis, increased activity of serum liver enzymes and mitogenic effects were observed in rat which might be related to a regenerative liver response to DDT [38].

2.1.5.2. Adverse Health Impacts of Endosulfan

Endosulfan is an organochlorine insecticide and acaricide used to control a broad range of insect and arthropod pests. Long term exposure to this pesticide is linked to immunosuppression, neurological disorders, congenital birth defects, chromosomal abnormalities, mental retardation, impaired learning and memory loss [39,40]. Endosulfan is a highly toxic chemical and poisonous to most living organisms. Documented human data have shown the central nervous system to be the major target of endosulfan action [41,42]. Endosulfan consists of two isomers, α -isomer and β -isomer. The latter is more toxic to both insects and mammals. It is carcinogen, teratogen and a male reproductive toxicant [41]. Studies on experimental animals showed that liver is one of the target organs of endosulfan toxicity [43]. Similar study revealed that endosulfan is nephrotoxic [44]. The main problems in productive toxicity of endosulfan in animal studies are decreased spermatozoon count and testosterone inhibition [45]. Dietary intake is expected to be the main source of endosulfan exposure to the general population. High level of exposure to endosulfan either intentionally or in contaminated food can be tremors and seizures, and even death [46]. The primary life-threatening effect produced following exposure to high levels of endosulfan is respiratory paralysis resulting from the development of refractory status epilepticus [40].

2.1.6. Organophosphate Pesticides

Organophosphate compounds are a group of pesticides that includes some of the most toxic chemicals used in agriculture [47]. The word "organophosphates" refers to a group of insecticides or nerve agents acting on the enzyme acetylcholinesterase responsible for facilitating

neurotransmission in many organisms [26]. Thus, organophosphate toxicity is due to the ability of these compounds to inhibit an enzyme, acetyl cholinesterase at cholinergic junctions of the nervous system. According to Kazemi and co-authors, the recorded death of 500 people each year in Golestan province of Iran was attributable to organophosphate pesticides [47].

2.1.6.1. Adverse Health Impacts of Organophosphates Pesticides

Increasing evidence from laboratory and field studies has shown that trace amounts of many organophosphates in the environment may cause significant endocrine disruption and reproductive disturbance or failure in invertebrates, fish, birds, reptiles and mammals [5].

Organophosphates in man act on the central nervous system by inhibiting acetyl cholinesterase and thus disrupt the nerve impulse by serine phosphorylation of the hydroxyl group in the active site of the enzyme [15]. It has been reported that organophosphorus insecticides are neurotoxic in nature by acting as inhibitors of neuronal cholinesterase activity and serum cholinesterase [6]. The organophosphate pesticides are also developmental neurotoxic. They inhibit the enzyme acetylcholinesterase which hydrolyses the neurotransmitter acetylcholine in both the peripheral and the central nervous system. This may lead to more permanent effects as acetylcholine has crucial functions during brain development [13]. Organophosphates poisoning may result in autonomic nervous system manifestations precedent occurrence of dizziness, headache, blurred vision, myosis, chest pain, increased bronchial secretions, and seizures. These parasympathetic effects are explained by the inhibitory action of these toxicant substances on cholinesterase activity [12].

Organophosphorus insecticides have also been described as potent alkylating agents and cause genotoxic effects. Epidemiological studies have reported that occupational exposure to organophosphate pesticides significantly increased chromosome damage [48].

Profenofos is a well known organophosphate pesticide which has been in agricultural use for controlling Lepidopteron pests of cotton and tobacco. Profenofos is extremely toxic to fish and it also toxic to humans [49]. Profenofos causes acute cytotoxic effects, decreases the cell growth rate causing dilation of nuclear membranes through inhibition of acetylcholinesterase an enzyme essential for the termination of nerve impulses [35,50]. Chlorpyrifos is also another organophosphate insecticide with broad spectrum which is reported to cause acute toxicity, carcinogenicity, teratogenicity and mutagenicity [50].

Nosiri *et al.* [30] studied the hepatotoxicity of Pirimiphos methyl organophosphate insecticide on Wistar Rats using the commercial formulation of the pesticide and found that the insecticide is hepatotoxic to the animal. They also implied that the insecticide can possibly have potential adverse effect on humans as they may be exposed during application, through water and food. However, the conclusion may be arguable as the amount in the commercial formulation and that in water or food items may not be the same. Second, test results obtained from experimental animals may not completely generalizable

to human. But still it is difficult to deny the possibility of hepatotoxicity of the insecticide on basis of the result unless some solid evidence is there is to refute it [30].

2.1.6.2. Mechanism of Toxicities of Organophosphate Pesticides

Organophosphate compounds which inhibit acetylcholinesterase leading to build up of acetylcholine at the acetylcholine receptor synapse; carbon disulphide which inhibits dopamine β -hydroxylase, manganese which inhibits dopamine formation by inhibiting tyrosine hydroxylase in the striatum are neurotoxic [7, 9]. Studies that have been conducted on many organophosphorus insecticides have similarly demonstrated the occurrence of oxidative damage [47]. Some organophosphate pesticides also affect the nervous system by inhibiting neuropathy target esterase which can result in a rare condition known as organophosphate induced delayed neuropathy [11]. Oxidative damage primarily occurs through production of reactive oxygen species including hydroxyl radicals and hydrogen peroxide that subsequently react with biological molecules as well as causing damage to membranes and other tissues [6]. Organophosphate toxicity is due to the ability of these compounds to inhibit an enzyme, acetyl cholinesterase at cholinergic junctions of the nervous system.

2.1.7. Carbamates Pesticides

Carbamate pesticides are derived from carbamic acid and kill insects in a similar fashion as organophosphate insecticides, but unlike organophosphate poisoning carbamate poisonings tend to be of shorter length because of reversibility of the inhibition of nervous tissue [51]. Like the organophosphates, their mode of action is inhibition of cholinesterase enzymes affecting nerve impulse transmission but they are relatively less toxic than organophosphates [26]. Carbamates are less persistent than organochlorines and organophosphates. However, carbamates action is fast and the kinetics of blocking is through the carbamylation of the enzyme by the covalent attachment of electrophilic groups steric carbamoyl sites of the enzyme [15]. Carbamates pesticides work against undesirable bugs by interfering with or inhibiting cholinesterase. Cholinesterase is one of many important enzymes needed for the proper functioning of the nervous systems of humans, other vertebrates, and insects. Although the effects of cholinesterase inhibiting products are intended for insect pests, these chemicals can also be poisonous or toxic to humans in some situations [7].

2.1.7.1. Adverse Health Impacts of Carbamates

Exposure to carbamate pesticides, which act as acetylcholinesterase inhibitors, can lead to reversible neurological disorders, and some are suspected of carcinogens and mutagens [36].

Carbamate pesticides like methomyl, carbonfuran, carbaryl, oxamyl methiocarb and thiodicarb are toxicant to mammals [51]. Methomyl is a broad-spectrum N-methyl carbamate insecticide with anti-cholinesterase activity which is highly acutely toxic by the oral route, moderately toxic by the inhalation route, and slightly toxic by the dermal route [52]. Methomyl induced toxicological effects in treated rats relative to control with the respect to

enzymes activity and histological changes in treated rats' organs [53]. Furthermore, carbofuran which is a carbamate has been reported to cause serious reproductive problems while occupational exposure to carbaryl, another carbamate pesticide, has been reported to result in nausea, vomiting, blurred vision, coma and difficulty in breathing [54].

2.1.8. Pyrethroids Pesticides

Pyrethroids originate from natural insecticide derived from pyrethrum extract derived from chrysanthemum flowers known as pyrethrins. Subsequently were obtained synthetically and are presently manufactured around 100 different commercial products [15]. Synthetic pyrethroid pesticides are non-polar to low-polarity lipophilic compounds and possess low mammalian toxicity and short-term environmental persistence [36]. They act on the central nervous system causing changes in the dynamics of the Na⁺ channels in the membrane of the nerve cell, causing it to increase its opening time prolonging sodium current across the membrane in both insects and vertebrates. These events can lead to neuronal hyper excitation [15].

2.2. Xenobiotic Heavy Metals

Heavy metals are a collective term which applies to the group of metals with atomic density greater than 4 g/cm³ or 5 times than that of water [16, 55]. Heavy metals are classified into two main categories as trace essential and toxic heavy metals. Trace essential heavy metals (i.e Cu, Zn, Cr, Fe, and Co) are required in very trace quantities for the proper functioning of enzyme systems, hemoglobin formation and vitamin synthesis in humans [56]. On the other hand, toxic heavy metals like Pb, Pd, Cd and Hg are not required by the body and thus they produce deleterious effects upon exposure even at very low concentrations [57].

2.2.1. Toxicities of Heavy Metals

Heavy metals are regarded as environmental pollutants due to their toxicity, persistence and bioaccumulation problem and their effects on health [58]. Heavy metals produce toxicity due to their potential to generate reactive oxygen and nitrogen species that disturb cell redox systems [16]. Lipids are most sensitive to oxidative modification by reactive oxygen species. According to Singh *et al.* [16], lipid peroxidation is as a major mechanism in the generation of diseases and disorders such as cancer, cardiovascular and neurodegenerative diseases that function through alteration of the integrity, fluidity, and permeability of membranes. Toxic heavy metals bring about greater variety of clinical conditions including fibromyalgia, chronic pain, osteoporosis, birth defects and autoimmune syndromes due to their free radical pathology which is worsen in the face of antioxidant deficits and metabolic acidosis [3].

Metals are emerging as an important class of human carcinogens. At least five transition metals like arsenic, cadmium, chromium (with oxidation of VI), beryllium, and nickel are accepted as human carcinogens in one form or another [3,59]. Cadmium(Cd), mercury(Hg), palladium (Pd) and lead(Pb) have got prime attention because of their bioaccumulation in living systems that can cause severe damage to the vital organs, namely reproductive

systems, nervous system, gastrointestinal tract, and mucous tissues [16]. Heavy metals can also bioaccumulate in the tissues of animals over time reaching cytotoxic concentrations in species with a long life span and occupying higher trophic levels of the food webs [60]. Tan *et al.*[60] treated toxic heavy metals in vitro with green turtle cell lines and the result of their study showed that the potential cytotoxicity of the metals. Heavy metals are known to cause oxidation of sulphhydryl groups of proteins, depletion of protein, DNA damage, lipid peroxidation, and several other effects due to their potential to produce highly reactive free radicals [20]. Heavy metals are among chemicals which may induce polyneuropathy and peripheral neuropathy. The typical symptoms include paresis, usually most pronounced peripherally in the upper and lower extremities [12]. Heavy metal compounds are among the most common environmental pollutants that cause neurotoxicity. Exposure to such chemicals may culminate in biochemical, physiological, morphological, functional, biophysical, pharmacological or behavioral changes which may be observed as the signs and symptoms of neurotoxicity [9]. It has been observed that exposure to heavy metals can negatively alter the function of the remaining functional nephrons of a patient with chronic kidney disease which may negatively affect the overall health of the patient [20].

2.2.2. Heavy Metals Exposure Routes

Heavy metal exposure can occur through contaminated air, food, water, or in hazardous occupation [10]. There are environmental (water, air, soil, dust), occupational, medicinal, and dietary sources of metal exposure [59]. Exposure may occur at the workplace, but environmental contamination of groundwater is also recognized as an important source of exposure that may result in kidney disease in populations without direct occupational exposure [14]. Fish is one of the most important food sources and thus, intake of trace elements from fish especially toxic elements is one of great concern for human health [61].

2.2.3. The Most known Toxic Heavy Metals

2.2.3.1. Mercury (Hg)

Mercury is one of the toxic heavy metals that occupy the top position on the list of hazardous substances [20]. Completer understanding of toxicities caused by mercury requires understanding forms of existence of mercury. Mercury exists mainly in forms of metallic elements, inorganic salts and organic compounds each of which possesses different toxicity and bioavailability [62]. These forms of mercury are present widely in water resources such as lakes, rivers and oceans where they are taken up by the microorganisms and get transformed into methyl mercury within the microorganism [34]. Methyl mercury is the most toxic form of mercury [9, 12]. Phenyl mercury, dimethyl mercury, and monomethyl mercury are also common forms of organic mercury. Of all organic forms of mercury, methyl mercury is encountered most frequently in the environment as it can be easily formed when inorganic mercuric ions are methylated by microorganisms present in soil and water [20]. Mercury is mostly present in the atmosphere as a gaseous element [62].

Various health impacts of Different Forms of Mercury

Symptoms attributed to high level exposure to metallic mercury include lung damage, mucous membrane changes, vomiting, diarrhea, nausea, skin rashes, hypertension, nephrotoxicity, and severe neurologic abnormalities [20]. Methyl mercury is a neurotoxic compound which is responsible for microtubule destruction, mitochondrial damage, lipid peroxidation and accumulation of neurotoxic molecules such as serotonin, aspartate, and glutamate [34]. Neurotoxic effects are mainly associated with the organic form of mercury following its accumulation in the motor regions of brain and central nervous system [20]. Being lipophilic, methyl mercury rapidly crosses the blood-brain barrier. It severely affects the central nervous system by causing psychiatric disturbances, ataxia, visual loss, hearing loss and neuropathy [12]. Human epidemics of methyl mercury toxicity have occurred during the 1950s and 1960s in Japan. Striking epidemics of fatal and non fatal neurologic disease were caused by methyl mercury exposure from sea food in Minamata Bay and fresh water fish in Nigat [9].

The brain remains the target organ for mercury, yet it can impair any organ and lead to malfunctioning of nerves, kidneys and muscles. It can cause disruption to the membrane and interrupt with intracellular calcium homeostasis. Mercury vapors can cause bronchitis, asthma and temporary respiratory problems [34]. High level of mercury can cause brain damages, heart, kidneys and affect the immunologic system [63].

The majority of human exposure to Hg is due to the ingestion of food contaminated with methyl mercury. Upon ingestion, it is absorbed readily by the gastrointestinal tract of humans. After about two weeks fraction of methyl mercury is oxidized to Hg^{2+} which enter systemic circulation where they can be delivered to target organ then causes severe nephropathy [20]. Mercury causes both tubular and glomerular damage. It is filtered by the glomerulus and reabsorbed in the proximal convoluted tubules resulting in tubular toxicity [14]. Mercury is established nephrotoxins at high exposure levels [19].

2.2.3.2. Lead (Pb)

Pb is a toxic metal which is found throughout the environment primarily due to various human activities [20]. Pb is a highly toxic metal whose widespread use has caused extensive environmental contamination and health problems in many parts of the world [34]. Some forms of organic lead can penetrate the skin easily and cross blood-brain barrier in adults causing them suffer from brain damage related to acute poisoning from organic lead compounds [62].

Toxic Lead exposure Routes

Lead is found in several industrial sources. Chief among these are the accumulator battery industry, lead smelters, lead or silver ore mining and lead refining. Non-industrial sources are air-borne lead from leaded gasoline fumes and lead-based paints [64]. Lead exposure from environmental and occupational sources still remains of great concern particularly in developing countries. Indeed, Africa's contribution to global lead pollution has risen from about 5 % in early 1980s to about 20 % a decade later [9]. In addition to industry, it has applications in fertilizers and pesticide for agriculture purposes, and in improving the

octane rating of gasoline in vehicular traffic systems [20]. Lead's exposure can occur from both anthropogenic and natural sources. In the environment, lead bioaccumulates in most organisms and is toxic to plants, animals and micro-organisms [65]. Environmental sources of Pb exposure include gasoline, contamination of food during processing, and contamination of air, soil, and water in areas close to old mines or garages [19]. The general public may be exposed to toxic lead through food, smoking, drinking water and domestic sources [34].

Lead Toxicities

A lot more is known about the neuro-behavioral toxicity of lead than any other environmental chemical. In fact, the recognition of lead as a neurotoxicant was discovered initially in the ancient world where classic signs of lead poisoning such as palour and palsy were recognized [9]. Pb^{2+} neurotoxicity is linked with presynaptic dysfunction. Presynaptic dysfunction has been identified in many neurological disorders and diseases including dementia, autism, bipolar disorder, Down syndrome, and schizophrenia [10].

Many studies revealed that lead is established nephrotoxic. According to Sarah and co-worker exposure to Pb may disrupt glomerular development which may result in renal insufficiency later in life [20]. Pb toxicity has been shown to cause mitochondrial swelling in the renal tubular cells and impairs energy production [19]. The 1968 study of 102 industrially exposed workers in Romania demonstrated that 17 had evidence of renal impairment when tested by discrete renal function tests such as creatinine clearance or urea clearance [64]. Acute nephrotoxicity toxicity of lead causes direct proximal tubular injury likely resulting from intranuclear, cytoplasmic and mitochondrial inclusion bodies composed of a lead-protein complex. Chronic lead exposure may result in hypertension, gout, and interstitial nephritis and fibrosis [14].

Generally, lead causes various dysfunctions. Acute exposure can cause hypertension, renal dysfunction, fatigue, sleeplessness, arthritis and hallucinations, and while chronic exposure can result in intellectual disability, birth defects, psychosis, autism, allergies, dyslexia, hyperactivity, paralysis, brain damage, kidney damage, and even death [20]. Pb exposure induces neurologic and hematological dysfunctions, renal and hepatic damage as well as reproductive disorders in the human body. Children are especially at greater risk because they have higher intestinal Pb absorption and more vulnerable nervous systems which are still under development [66].

Mechanism Pb toxicity

Lead induced toxicity is mediated by enhancing the production of free radical compounds such as hydroxyl, superoxide, nitric oxide and peroxy nitrite radicals [16]. Pb interferes with the process of neurotransmission from one cell to another at a synapse by blocking conductance through neuronal calcium and K^+ channels as well as responses to activation of acetylcholine, adrenergic, angiotensin and glutamate receptors [9].

The ionic mechanism of lead toxicity also occurs mainly due to the ability of lead metal ions to replace other bivalent cations. The ionic mechanism of lead toxicity causes significant changes in various biological processes such as cell adhesion, intra- and inter-cellular

signaling, protein folding, maturation, apoptosis, ionic transportation and enzyme regulation [34].

2.2.3.3. Cadmium (Cd)

Cadmium is toxic to humans, animals, micro-organisms and plants. Although a small amount of cadmium intake is absorbed by the body and stored, evidences showed even very low cadmium exposure may give rise to skeletal damage due to osteoporosis and fractures [62]. Dinis and Fiuza [62] indicated that low level exposure to Cd usually does not produce immediate health effects, but may cause severe health problems over long periods. Because the biologic half-life of cadmium is long, prolonged low level exposure leads to excessive accumulation in certain tissues especially the kidney [64]. Inhalation of cadmium dust or smoke may cause dryness of the throat, headache, chest pain, coughing, increased uneasiness and bronchial complications [62].

Exposure Routes to Cd

Sources of Cd exposure in the general population are cigarette smoke, ingestion of polluted vegetables, and breathing air from fuel combustion [19,64]. Because of the high concentration of Cd in tobacco, individuals who smoke tobacco products are exposed regularly to this metal. Indeed, most cigarettes contain approximately 10% of Cd contained in it [34].

Industrial uses of Cd include manufacture of batteries, pigments, coatings, and plastics. Additionally, the use of this metal in phosphate fertilizers can leave soil and water contaminated heavily with Cd residue [20].

Various Dysfunctions Caused by Cd

Cadmium and lead are two of the most prevalent as well as two of the most nephrotoxic metals known to man. Both cadmium and lead are nephrotoxic and can lead to progressive renal failure [19,64]. Kidney is one of the primary targets of Cd intoxication. Renal accumulation of Cd leads to reduced glomerular filtration rate, polyuria, and generalized tubular dysfunction. Thus, the metal is nephrotoxicant [20]. Chronic low exposure to Cd can cause both renal proximal tubular damage and decline in glomerular filtration rate in experimental animal models. Human and animal studies reported that Cd may potentiate or exacerbate diabetic nephropathy [19]. Clinically, cadmium nephrotoxicity presents with features of proximal tubular dysfunction such as glucosuria, aminoaciduria, and low molecular weight proteinuria [14]. Like lead, cadmium is proved to have mutagenic and carcinogenic effect [67]. Cadmium concentration increases 3,000 fold when it binds to cystein-rich protein such as metallothionein. In the liver, the cystein-metallothionein complex causes hepatotoxicity and then it circulates to the kidney and gets accumulated in the renal tissue causing nephrotoxicity [34].

Cd toxicity is associated with pulmonary, renal, hepatic, skeletal, reproductive and cardiovascular dysfunctions. This non-essential metal is also classified as a group I human carcinogen by the International Agency for Research on Cancer [66]. The best characterized example of intoxication of a large population by environmental exposure to cadmium is "itai-itai-byo" or "ouch-ouch" disease, so named because of the crippling and painful osteomalacic component. The disease was endemic to the Jinzu River basin of the Toyama Prefecture in Japan, with peak incidence shortly after World War II and was

attributed to cadmium overload from a zinc mine upriver [64].

2.2.3.4. Arsenic (As)

It is often referred to as a metalloid because of its chemical and physical properties which are intermediate between metals and non-metals [34]. As stated by Jaishankar *et al.*[34] arsenic can exist in the form of oxides, sulfides or as a salt of iron, sodium, calcium, copper, *etc.* Humans may encounter arsenic by natural means, industrial source, or from unintended sources. In reducing and oxygenated conditions, arsenite, and arsenate, are the main oxidation states [68]. Arsenite and arsenate are the most common inorganic forms of As in water while arsenobetaine, arsenocholine, and arsenosugars are the important organic forms in certain foods, particularly in sea foods [69]. In water, it is most likely to be present as arsenate with an oxidation state of 5, if the water is oxygenated. However, under reducing conditions it is more likely to be present as arsenite, with an oxidation state of 3. The gaseous form of arsenic called Arsine is considered to be the most toxic form followed by the arsenites (As (III)), the arsenates (As (V)) and organic arsenic compounds [27]. Drinking water may get contaminated by use of arsenical pesticides, natural mineral deposits or inappropriate disposal of arsenical chemicals. The intermediate product of monomethylarsonic acid produced by biotransformation is not excreted through urine which is found to be highly toxic compared to other arsenicals. It is potentially accountable for arsenic-induced carcinogenesis [34].

Health impact of As

Arsenic is known to be a carcinogen in humans; it is well documented to cause cancer of the skin, lungs, urinary bladder, kidney and liver [70]. The International Agency for Research on Cancer (IARC) classifies arsenic as a class 1 carcinogen [71].

When humans are chronically exposed to arsenic through their drinking water, they exhibit increased rates of several cancers such as bladder, liver and kidney cancers and cancers of other internal organs [69,72]. Arsenic has been shown to be embryotoxic and teratogenic in animals, acting through foetal growth retardation and neurotoxicity [73]. In Furthermore, chronic health effects of cardiovascular, pulmonary, nervous, endocrine and reproductive problems [74]. Chronic oral exposure to elevated levels of inorganic arsenic in humans has resulted in gastrointestinal effects, anemia, peripheral neuropathy, skin lesions, hyperpigmentation, gangrene of the extremities, vascular lesions, and liver or kidney damage [75].

Arsenic, a protoplasmic poison, primarily affects the sulphhydryl group of cells leading to malfunctioning of cell respiration, cell enzymes, and mitosis [20]. Elevated arsenic exposure also appeared to adversely affect the developing immune system including both T cell and B cell-associated immune functions. Maternal arsenic exposure seemed to reduce T cells in placenta and cord blood and increase nonspecific antibody production by B cells in children at 9 years of age [9].

Mechanism of Toxicity of As

Arsenic is a protoplasmic poison since it affects primarily the sulphhydryl group of cells causing malfunctioning of

cell respiration, cell enzymes and mitosis. Biotransformation of inorganic arsenic species forms methylated arsenicals which are the end metabolites and the biomarker of chronic arsenic exposure. The end product of biomethylation is methylated inorganic arsenic such as monomethylarsonic acid and dimethylarsinic acid [34].

2.3. Xenobiotic Polychlorinated Biphenyls

Polychlorinated biphenyls (PCBs) are a group of 209 possible congeners with different numbers and positions of chlorine atoms on the aromatic rings [35]. Congeners are defined as individual PCBs that are members of a homologous series of chlorinated biphenyls [76]. The PCB congeners are sometimes separated into two categories, "dioxin-like" or "non-dioxin-like," that are defined by structural differences and that act by different toxicological mechanisms. The dioxin-like PCBs are structurally and toxicologically related to the chemical 2, 3, 7, 8- tetrachlorodibenzo-p-dioxin [77]. PCBs are a group of synthetic organic chemicals that can cause a number of different harmful effects [78].

PCBs are a family of industrial chemicals that were produced in the United States from 1929 to 1979 and used primarily as insulating fluids in capacitors, transformers, and other electrical equipment [79]. PCBs have been used in industry as dielectric fluids in capacitors and transformers, plastisizers, flame retardants, lubricants and heat transfer fluids [35].

PCBs can still be released into the environment from poorly maintained hazardous waste sites; improper dumping of PCB wastes such as old transformer fluids; leaks or releases from electrical transformers containing PCBs; and disposal of PCB-containing consumer products into municipal or other landfills [78]. PCBs in the environment may be expected to associate with the organic components of soils, sediments and biological tissues, or with dissolved organic carbon in aquatic systems rather than being in solution in water [29]. Due to their persistent nature, PCBs remain widely distributed in the environment, and they are also present at many pristine areas [80]. Some compounds in PCBs are considered as Persistent Organic Pollutants (POP) because of their chemical stability, lipophilicity and consequently their ability to bioaccumulate in the environment [81].

Adverse Health Impacts of PCBs

PCBs suppress the human hormonal and immune systemic; disturb behavior and reproductive system of animals. They are known to cause cancer and birth defects [4,78]. Contamination of rice oil by PCBs in Japan in 1968 and Province of Taiwan in 1979 has resulted in the exposure of a large number of people to PCBs and their contaminants. Children born up to 7 years after maternal exposure in the Taiwan incident had hyper pigmentation, deformed nails and natal teeth, intrauterine growth delay, poorer cognitive development, behavioral problems and higher activity levels. Adult victims had reproductive dysfunction, severe chloracne, hyper pigmentation, visual disturbances and respiratory problems [5,29]. Few epidemiological studies of occupationally exposed workers have indicated an increased incidence of cancer of the liver and of the biliary tract. However, in all of these studies the exposure occurred to commercial PCB

mixtures, the compositions of which clearly differ from those of PCBs in food [8]. A large body of health effects research comes from children born to mothers who were exposed to high concentrations of a mixture of PCBs and polychlorinated dibenzofurans in accidental poisoning incidents in Taiwan and Japan [82]. These prenatally exposed children exhibited a number of adverse health effects including neurodevelopment effects such as cognitive deficits, developmental delays, effects on motor skills, behavioral effects, immunological effects, and skin alterations ranging from irritation to chloracne a potentially serious inflammatory condition [78,83]. Prenatal PCB exposures have also been associated with immunological effects such as increased infections, in multiple epidemiological studies with supporting evidence from the literature on effects of dioxin-like chemicals [13,84].

Prospective studies have documented that low level exposures to PCBs can impair the neurobehavioral development in children. Now days, an ample evidence exists concerning neurotoxicities of PCBs to adult individuals [13]. There is growing evidence that exposure to nanogram levels of PCBs can disrupt normal metabolism of sex hormones in fish, birds and mammals. This in turn, may lead to reproductive dysfunction such as reduction in fertility, alternation of sex behavior and viability of offspring [5]. Overall, the critical endpoints for risk assessment of PCBs are identified as cancer, immunotoxic and behavioral effects [8].

2.4. Persistent Organic Pollutants (POPs)

Persistent, fat-soluble chemical contaminants commonly referred to as the Persistent Organic Pollutants (POPs). POPs are defined as highly toxic compounds, persistent in the environment, able to migrate in food chains and have high bio-accumulation potential [4]. Because of persistence, bioaccumulation and lipophilic nature, POPs are often ubiquitous in the environment and thus they can be detected even in pristine areas [3,85]. POPs are typically lipophilic compounds with low water solubility that are resistant to environmental breakdown and accumulate in adipose tissue. They bioconcentrate in fish, wildlife and human tissues. The highest levels are found in marine mammals [29] The United Nations Environment Programme listed 12 POPs under the Stockholm Convention of POPs for global action. These 12 compounds consist of four unintentional POPs including dioxins, furans, hexachlorobenzene, PCBs and eight intentionally produced pesticides including aldrin, chlordane, DDT, dieldrin, endrin, heptachlor, mirex and toxaphene [86]. Most POPs are organochlorine pesticides, namely, aldrin, endrin, chlordane, DDT, heptachlor, mirex, toxaphene and hexachlorobenzene. They have been banned for agricultural or domestic uses in Europe, North America and many countries of South America in accordance with the Stockholm Convention. However, some organochlorine pesticides are still used e.g. DDT is used to control malaria in some developing countries [29].

Health Impacts of POPs

Growing body of epidemiologic, animal and research studies suggest a link between long-term exposure and abnormal growth and development; impaired neurobehavioral development/functions; cancer and increased susceptibility

to infections [29]. For instance, dioxins are considered responsible for causing birth defects, immunotoxicity, tumor production, changes in metabolism and death [1]. The term dioxin refers to a family of related chemical compounds that include the chlorinated dibenzo-p-dioxins and chlorinated dibenzofurans which form a class of compounds called polychlorinated diatomic hydrocarbons. Dioxin production seems inevitable whenever combustion of organic matter occurs in the presence of chlorine. Dioxins and furans are transported from place to place mainly in the atmosphere [35]. Dioxins are one of the most toxic human-made compounds which are known human carcinogen. Many organochlorine compounds such as DDT, PCBs and dioxins are considered as endocrine disrupters [87]. Research studies show the genotoxicity of POPs. Genotoxic compounds are those that act directly or indirectly on the DNA.

The genotoxic potential is a primary risk factor for chronic or long-term effects such as reproductive effects and toxicity [15]. Following the Seveso disaster in northern Italy in 1976, a remarkable increase in the proportion of girls was reported among offspring of heavily dioxin exposed men [18]. POPs are pro-oxidants that induce excessive consumption and wasting of glutathione and ascorbate. These two antioxidants are at the center of the antioxidant recycling network that protects delicate cell components from free radical oxidative damage when we are in physiologic homeostasis and immune tolerance [3].

3. Challenges that Cast Shadow on Xenobiotics' Study Results

3.1. Xenobiotics Interaction

The interactions between different chemical components in a mixture may result in either a weaker (antagonistic) or a stronger (synergistic) combined effect than the additive effect [88]. A synergistic effect occurs when the combined effect of two chemicals is greater than the sum of the effects of each chemical given alone while an additive effect occurs when the combined effect of two chemicals corresponds to the sum of the effects of each chemical given alone [89]. The strongest interaction found in the literature was a 5-fold increase in the neurotoxicity of hexane when methyl isobutyl ketone was co-administered.

An antagonistic effect occurs when the combined effect of two chemicals is less than the sum of the effects of each chemical given alone [59]. In fact, antagonistic interactions among xenobiotics have a positive impact unlike additive and synergistic interactions.

Thus, it is true that mixtures of pesticides can produce additive or synergistic effects or even can produce antagonistic effects [50]. Shaik and co-workers treated human peripheral blood lymphocytes with the pesticides and their combinations. The authors' *in vitro* experiment showed that the combination of the pesticides led to additive and synergistic effects. Based on the results, endosulfan and chlorpyrifos caused synergistic toxicity; chlorpyrifos and profenofos caused additive toxicity while combination of endosulfa and profenofos showed antagonistic toxicity. The living organisms in nature are

frequently exposed to a mixture of xenobiotics simultaneously. The combined interactions between xenobiotic substances can worsen the impact of xenobiotics on health.

Similarly, combined exposure to Cd and ethanol has been shown to produce increased level of norepinephrine in hypothalamus and mid brain of rats in comparison to the rats exposed to only Cd. The synergistic effect of lead and mercury are extremely neurotoxic and has been reported to be much worse than the single one [16].

3.2. Presence of Adjuvants

Pesticides are used throughout the world as mixtures called formulations. They contain adjuvants in addition to the active principle. An adjuvant is an additive or supplement used to enhance the performance or aid in the stability of formulations of active ingredients [90]. These supplementary chemicals in pesticide formulation are often kept confidential to the manufacturing companies. The purpose of addition of such chemical is for further enhancement of the activity of the active principle [91]. Mesnage *et al.* [91] treated hepatic human cell lines *in vitro* with phosphoglycine, phenylurea, synthetic auxin, pirimicarb, neonicotinoid, neonicotinoid, triazole and imidazole pesticides' formulations and active principles separately. They confirmed the potential cytotoxicities of the formulations and active principles by the measurement of apoptosis and necrosis. The results of their study showed that all formulations (except one) were cytotoxic far more than their active principles.

The implication is that toxicity results obtained merely from pesticide active principles or standards do not necessarily indicate the extent of seriousness of the toxicity of the pesticide formulations. Numerous studies have found that pesticide active ingredients elicit very different physiological effects on non-target organisms when combined with their co-formulants and tank adjuvants [92].

3.3. Detection Problem

Adverse effects on human health can begin at thresholds below direct detection. In the case of dioxin, PCB, polybrominated biphenyl, and related compounds human health risks emerge at the parts per trillion levels. This is in contrast to most laboratory tests that are only able to measure down to parts per million levels of detection [3].

4. Conclusion

The paper depicts several environmental xenobiotics, their health impacts and routes of exposure. We are being exposed to myriads of such chemicals though dietary, inhalation from air and occupational exposures. Unless we take proper precaution in prevention of toxic exposures individually and safety and regulation standards are seriously followed by governments, the overwhelmed burden of chronic diseases due to such chemicals is alarming.

On top of this, xenobiotics may exist in the environment in different mixture. Some xenobiotics interact synergistically that they impose health problems many times greater than

that predicted they would exist alone. As a result, the documented health impacts for a single compound may not necessarily indicate the seriousness of the problem in presence of interaction. Furthermore, xenobiotic pesticide formulations contain adjuvants in addition to their active ingredients.

The implication is that the toxicity study result of active ingredient alone does not reveal the real toxicity of the formulation.

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