Environmental Xenobiotics and Its Effects on Natural Ecosystem

1

Asha Embrandiri, S. Katheem Kiyasudeen,
Parveen Fatemeh Rupani,
and Mahammad Hakimi Ibrahim

Abstract

Environmental contamination by xenobiotics is a worldwide phenomenon as a result of human activities resulting from rise in urbanization and population growth. There are numerous sources of xenobiotics ranging from pharmaceuticals to agriculture. Recently, the demand for pharmaceuticals versus population growth has placed the public at risk. In addition, the making of unlawful drugs has led to the discharge of harmful carcinogens into the water system. The release of these harmful pollutants results in numerous short- and long-term effects to the natural ecosystem. This review takes a look at the sources of xenobiotics, their fate in the ecosystem and means of action with possible prevention methods.

Keywords

Xenobiotics • Carcinogens • Degradation

1.1 Introduction

Since the time of the Industrial Revolution, scientific and technological developments permitted humans in the over utilization of resources creating disturbance to the natural ecosystem (Sikandar et al. 2013). The generation of huge amount of toxic substances released from industrial processes caused widespread contamination of the ecosystem. The major contaminants are halogenated and nitrated hydrocarbons (Jain et al. 2005). Several herbicides, insecticides and fertilizers used in

A. Embrandiri (✉) • S.K. Kiyasudeen • P.F. Rupani • M.H. Ibrahim
School of Industrial Technology, Universiti Sains Malaysia,
Gelugor, Penang 11800, Malaysia
e-mail: ashanty66@gmail.com

A. Singh et al. (eds.), *Plant Responses to Xenobiotics*,
DOI 10.1007/978-981-10-2860-1_1

agricultural activities as well as synthetic compounds are produced from industrial activities, namely, pharmaceuticals, agrochemicals, dyes, solvents, halogenated compounds, hydraulics, fire retardants, pigments, etc. (Reineke and Knackmuss 1988). Pharmaceutical wastes have become well known sources of prolonged environmental contamination due to the continous use in anthropoid and veterinary medications. These chemicals are believed to have specific mode of action in the body. The chemical composition of pharmaceuticals lead to possible effects on aquatic flora and fauna as compared to other chemical compounds. However, pharmaceuticals are proposed to pose only a low risk for acute toxicity in the environment. For chronic effects, the situation may be different; nevertheless, there is a considerable lack of information for the chronic effects and its risk of toxicity. In addition, there is little or no informationregarding multi generational life cycle effects, knowing that exposure to toxicity in many aquatic organisms happen during their entire life (Fent et al. 2006). Accordingly, various environmental analyses reported that the drug residues in surface water and treated wastewater are widespread. These chemical compounds that arise from industries are xenobiotics. Xenobiotic compound is persistent in the environment with toxicity effect making them potential health hazards leading to significant impacts on the ecosystem. Therefore, researchers need to focus more on effects of pollution and its prevention techniques.

1.2 Xenobiotics: Sources and Types

Originally, the term xenobiotic comes from the Greek word xenos, which means foreign or strange, and ‘bios’, which means life. Xenobiotics are chemical compounds exhibiting abnormal structural characteristics (Fetzner 2002). The unusual presence of any substance in high concentrations can also be regarded as xenobiotics, for instance, the presence of antibiotic drugs in the human body which may not be produced by the body itself nor is a normal part of diet. At times, a natural substance can be defined as a xenobiotic if it found its way into humans or other animals. Bonjoko (2014) proposed the word ‘xenobiotic’ based on the physiological and biological effects of exogenous substances whether natural or synthetic (drugs, chemicals) on the cells, tissues or organs of the organisms.

Many xenobiotics are potientially hazardous to the organisms which are exposed to them in the environment. However, bioavailabilities of such substances are dependent upon the characteristics of the organism, the chemical, and the environment. Maenpaa (2007) reported that the toxicity of any xenobiotic is related to the bioaccumulated chemical residue in the organism. Xenobiotics may persevere for long term (months to years) in the environment. For example, the polymer structure of lignin, or the constituents of the cell wall of the spores of a few fungi (melanin polymers), may not degrade rapidly in the natural environment (Fetzner 2002). Similarly, in aquatic environments, hydrophobic pollutants which are eventually

stored in sediments become hazardous on exposure to benthic organisms. Any exposure to the sediments contaminated by xenobiotics possibly affects the lower trophic levels. It may also result in biomagnification or more serious toxic effects at higher trophic levels (Landrum and Robbins 1990; Lee II 1992; Streit 1992; Newman 1998).

New technologies to determine trace polar compounds have helped to give new insights on the removal of xenobiotics. In the beginning, pharmaceutical products were reported in treated wastewater in the USA, with the range of about 0.8–2 μg/L (Garrison et al. 1976). Thereafter, the UK reported 1 μg/L of clofibric acid in the rivers (Richardson and Bowron 1985). In 1986, Rogers (from Canada) identified the concentration of naproxen and ibuprofen in wastewaters. Accumulation of diclofenac, a pain killer which was used by veterinarian to treat cattle, significantly reduced the population of Asian white-backed and Indian vultures (9 from 150 in 1997 to 25 in 2010) nesting in Keoladeo Natural Park in North Western India. The Geological Survey Department (United States) reported traces of many different drugs and toiletries as well as steroids, insect repellants and phthalates in the water supply. Even though the concentrations were in traces, the effect of chronic exposure can be unpredictable. For example, production of bulk drugs has been recently identified as an important source of environmental pollution which consists of active pharmaceutical elements in certain locations (Gunnarsson et al. 2009; Fick et al. 2010). Also, there are raising concerns worldwide on the pharmaceutical residues found in surface water which can have effects on aquatic organisms. Therefore, there is a major challenge in developing lucid strategy for prioritizing drugs on which to focus the most extensive environmental research efforts for (Fick et al. 2010).

1.3 Sources of Pharmaceutical-Based Xenobiotics

There are different synthesized chemicals present in the environment which may have different interactions with the exposure to humans and the ecosystem. However, the details of these impacts are not adequately studied or understood. Among the different pharmaceutical substances, pharmaceutical active compounds (PhACs) are xenobiotic-based elements that entered the environment as the parent compound or as pharmacologically active metabolites (Bonjoko 2014). PhACs are considered as potentially toxic compounds that are largely used in agriculture and industry. However, for many years the researches were based on the pharmaceutical regulations which were of interest by drug organizations, and less attention was paid on the toxicity and its environmental issues (Jones et al. 2001).

Environmental pharmaceutical persistent pollutants (EPPPs) are the components which are available in waterbodies all over the world. Not much literature is available about the possible negative effects and impacts of EPPP in humans and the environment. Bonjoko (2014) reported that EPP's exposure may cause extinction of species and imbalance of sensible ecosystems (EPPS affect the reproductive

systems of, e.g. frogs, fish and mussels). For example, in sewage plants of pharmaceutical industries, large amount of antibiotics and other pharmaceutical compounds have been found. According to the European Union (EU), about 3000 different substances were found in downstream that were used in human medicine such as antibiotics, beta-blockers, analgesics and anti-inflammatory drugs and many others. Likewise, a large number of pharmaceuticals are used in veterinary medicine such as antibiotics and anti-inflammatory (Fent et al. 2006). Bonjoko (2014) explained the potential routes of entry of pharmaceutical and household care products in the environment. It includes:

1. Through patient excretion
2. Direct release into the wastewater system from manufacturing, hospitals or disposed through toilets and sinks
3. Terrestrial depositions, i.e. irrigation with treated and untreated wastewater, sludge application to land, leaching from solid waste landfills
4. Non-pharmaceutical industrial sources, i.e. plastic products
5. Agricultural wastes such as herbicides, pesticides and fertilizers
6. Through ageing infrastructures, i.e. synthetic compounds such as analgesics and antihistamines which were exposed in streams and rivers
7. Drugs associated with plant health
8. Herbal preparations and their interaction with the environment

1.4 Fate/Biodegradation of Xenobiotic Compounds

Xenobiotics with the presence of microbes can undergo biodegradation process depending on the microbe's species and the xenobiotic compounds.

Xenobiotic metabolism undergoes a biochemical modification of pharmaceutical substances (xenobiotics) by living organisms, which usually occurs through specialized enzymatic systems. Enzyme like cytochrome P_{450} secreted in the liver helps in the degradation process and thus excreted by urination, exhalation, sweating and defecation. Biodegradation and oxidation of a parent compound happen to form carbon dioxide and water. Each stages in the degradation pathway is catalysed by a specific enzyme produced by the degrading cell. However, degradation of some xenobiotics depends on its specific compound structure, which includes the required enzymes, for example, oxygenases. These enzymes are metabolized to provide energy as well as reducing equivalent for the degradation process (Bonjoko 2014). Figure 1.1 illustrates the possible environmental fate of a xenobiotic compound.

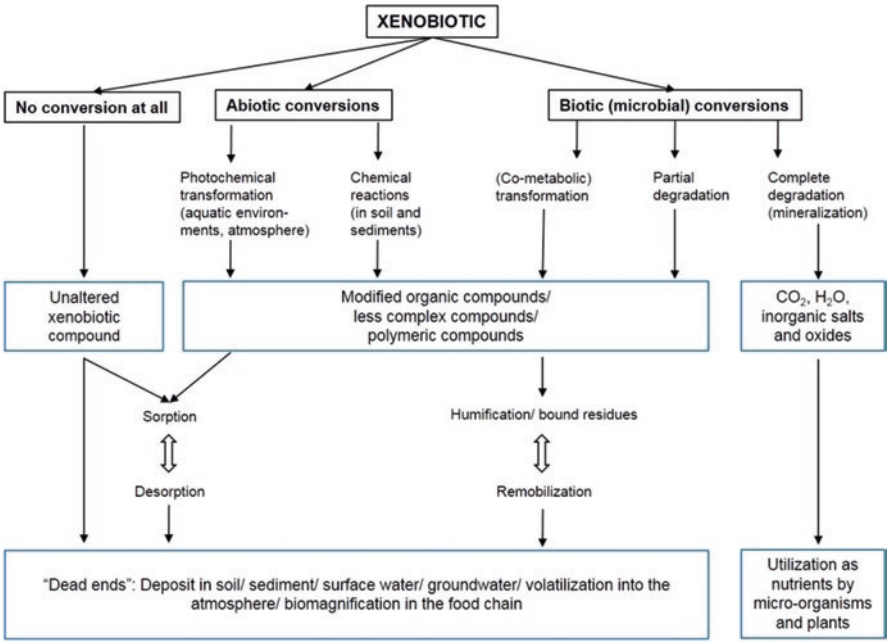

Fig. 1.1 Possible environmental fate of a xenobiotic compound

1.5 Common Xenobiotic Compounds Based on Its Course of Action

Xenobiotics are designed to target specific metabolic and molecular pathways in humans and animals in the ecosystem. However, when xenobiotics are introduced into the environment, they may affect the same pathways in animals having identical or similar target biomolecules, organs, tissues or cells. The current ecotoxicological effects of pharmaceuticals deal mainly with the acute toxicity in standardized tests and it is generally focused on aquatic organisms. The influence of environmental parameters such as pH on toxicity has only rarely or not yet been investigated. More studies have focused on acidic pharmaceuticals that may induce different toxicities depending on speciation at different ambient pH. Moreover, till date less research has been done on the effects of drug metabolites. The following are the common pharmaceutically based xenobiotic compounds that pose such environmental concerns. Figure 1.2 illustrates the different types of pharmaceutical xenobiotics.

1.5.1 Analgesics and Non-steroidal Anti-inflammatory Drugs (NSAIDs)

The widely used non-steroidal anti-inflammatory drugs (NSAIDs) ibuprofen, naproxen and diclofenac and some of their metabolites such as hydroxyl-ibuprofen and carboxy-ibuprofen are widely used and usually can be detected in surface and

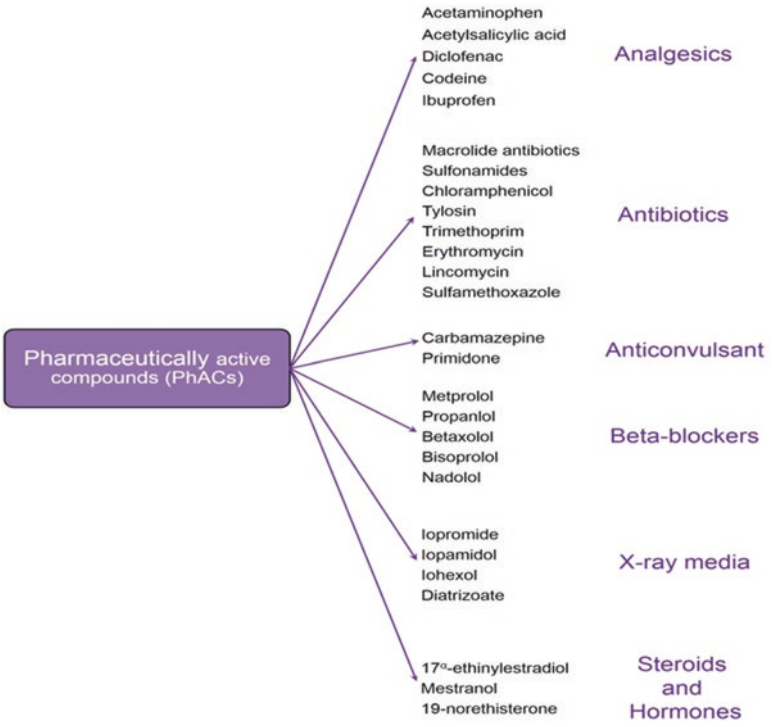

Fig. 1.2 Different types of pharmaceutical xenobiotics

water sewage. Gross et al. (2004) reported that NSAID levels exceed in sewage system to 1 μg/L, and it can exceed the concentration to 0.1 μg/L in the effluent of conventional sewage plants (mechanical clarification and biological treatment) in the USA. The deacylated which is a more active form of acetylsalicylic acid has detected in many municipal wastewaters at the levels up to 4.1 μg/L, 13 μg/L or even 59.6 μg/L. Similar to acetylsalicylic acid, acetaminophen (paracetamol) is well removed from STP. However, Kolpin et al. (2002) reported that up to 10 μg/L (median 0.11 μg/L) acetaminophen is spotted in 24 % of samples from US streams (Kolpin et al. 2002). Also, the analgesic codeine was detected in 7 % of samples (median 0.01 μg/L). Moreover, in many countries, diclofenac was frequently detected in the wastewater and also in lower levels of surface water.

Wiegel et al. (2004) have reported that in Norway, ibuprofen and its metabolites have been found in all sewage samples and in seawater at the concentrations of 0.1–20 μg/L. Kolpin et al. (2002) detected ibuprofen in 10 % of stream water samples in high concentrations up to 1 μg/L (median 0.2 μg/L). Moreover, several other NSAID compounds have been detected in sewage and surface water as well as in drinking water samples and groundwater.

1.5.1.1 Mode of Action

NSAIDs (non-steroidal anti-inflammatory drugs) are frequently used to treat inflammation and pain and to relieve fever, and sometimes they are also used for long-term treatment of rheumatic diseases. NSAIDs act by inhibiting factor either reversibly or irreversibly one isoform of the cyclooxygenase enzyme (COX-1 and COX-2), which catalyse the synthesis of different prostaglandins from arachidonic acid. COX-1 and COX-2 inhibit by classical NSAID at different degrees, whereas new NSAID act more selectively on COX-2, the inducible form which is responsible for the inflammatory reactions. Differences in binding site size are in charge for the selectivity of these drugs. NSAID inhibit nonspecifically.

In the kidney, prostaglandins are elaborate in maintenance of the equilibrium between vasoconstriction and vasodilatation of the blood vessel that supply glomerular filtration.

At times, after chronic NSAID treatments, renal damages or renal failure seems to be triggered by the lack of prostaglandins in vasodilatation-induction. Inhibition of both COX isoforms can cause gastric damages. In contrast, liver damages are apparently due to building of reactive metabolites (e.g. acyl glucuronides) rather than inhibition of prostaglandin synthesis (Bjorkman 1998). The mode of action of paracetamol is not yet fully elucidated. However, it has been found that this drug acts mainly by inhibiting the cyclooxygenase of the central nervous system, and it does not have anti-inflammatory effects, because of the lack of inhibition of peripheral cyclooxygenase involved in inflammatory processes. Adverse effects of paracetamol mainly occur when the availability of glutathione is diminished in liver cells which could be due to formation of hepatotoxic metabolites, primarily *N*-acetyl-*p*-benzoquinone.

1.5.2 Blood Lipid Regulators

The most frequently reported pharmaceutical in monitoring studies is clofibric acid which is an active metabolite from a widely used blood lipid regulators such as clofibrate, etofylline clofibrate and etofibrate. These compounds have been found in numerous wastewaters, surface waters and seawater and at rather high concentrations in drinking water (0.07–0.27 μg/L) and groundwater (4 μg/L). Bezafibrate and gemfibrozil which are lipid-lowering agent have been found in maximal concentrations of up to 4.6 and 0.79 μg/L, respectively, in wastewater and surface water, respectively (Kolpin et al. 2002). In addition, other drugs which act as metabolite of fenofibrate such as gemfibrozil, clofibric acid and fenofibric acid have also been detected in sewage up to the μg/L level and in surface water (Heberer 2002).

1.5.2.1 Mode of Action

There are basically two types of antilipidemic drugs, namely, statins and fibrates, which are used to decrease the concentration of cholesterol (statins and fibrates) and triglycerides (fibrates) in the blood plasma. These drugs have been targeted analytically more often in the aquatic environment. Statins as inhibitors of cholesterol

synthesis act by inhibiting the 3-hydroxymethylglutaril coenzyme A reductase (HMG-CoA), responsible for the limiting step in the cholesterol synthesis, namely, the conversion of HMG-CoA to mevalonate. Due to interactions of statins with mevalonate metabolism, multiple additional effects occur (anti-inflammatory, antioxidative). Studies also show that statins affect juvenile hormone synthesis in insects as fluvastatin completely suppressed its biosynthesis in vitro and in the mandibular organ of lobsters. The effects of fibrates lead to alterations in transcription of genes encoding for proteins controlling lipoprotein metabolism and they also activate the lipoprotein lipase enzyme, which is mainly responsible for the conversion of very-low-density lipoprotein (VLDL) to high-density lipoproteins (HDL), decreasing therefore plasma triglyceride concentration.

Moreover, fibrates stimulate cellular fatty acid uptake by conversion to acetyl-CoA derivatives and catabolism by the beta-oxidation pathways. Hence, these processes are combined with a reduction in fatty acid and triglyceride synthesis that decreases in VLDL production. Studies on animal (rat) show that hepatic damages can occur after chronic exposure to fibrates and which could be due to the inhibition of mitochondrial oxidative phosphorylation. Fibrates caused in rodents a massive proliferation of peroxisomes. Strong correlation between fibrate exposure and hepatocarcinogenicity in rodents was found, while this was not observed in humans (Cajaraville et al. 2003). These findings increase the interest for ecotoxicological impact of this therapeutic class of drugs. Activators of PPARα genes (found in fishes) include different endogenously present fatty acids, leukotrienes and hydroxyeicosatetraenoic acids and drugs, such as fibrates.

1.5.3 Beta-Blockers

Several beta-blockers such as bisoprolol, propranolol and metoprolol were identified in wastewater showing 0.59, 2.9 and 2.2 μg/L, respectively. Also in lower concentration, other beta-blockers, namely, nadolol (in surface water) and betaxolol (0.028 μg/L in surface water), were detected (Ternes 1998). Moreover, Sacher et al. (2001) reported the presence of propranolol, metoprolol and bisoprolol in surface water and sotalol in groundwater.

1.5.3.1 Mode of Action

Beta-blockers act by competitively inhibiting beta-adrenergic receptors. They are employed for the treatment of high blood pressure (hypertension) and the prevention of heart attacks in high-risk patients. Regular body processes like heartbeat regulation and oxygen supply, vasodilatation of blood vessels and bronchodilation are the functions of the adrenergic system. Furthermore, it is important for the metabolism of carbohydrates and lipids in cases of starvation. Beta-blockers could selectively impede one or more β-receptor types based on their needs. For instance, β2-blockers are employed for the treatment of hypertension preventing impending cardiac arrests, as this receptor subtype is not present in the heart. Beta-blocker

propranolol, a beta1-adrenoceptor antagonist, has the ability to stabilize cell membranes, unlike metoprolol which does not have that property (Doggrell 1990). Side effects of these beta-blockers are mostly bronchoconstriction and disturbed peripheral circulations. They are supposed to pass the blood-brain barrier and to act in the central nervous system because of their lipophilicity (Heberer 2002). Clenbuterol or ractopamine that functions in mammals as β-agonist had a different reaction in rainbow trouts. The different structures and function of the receptors may be responsible for varied affinity with β-blockers and mechanisms triggered by these drugs.

1.5.4 Neuroactive Compounds (Antiepileptics and Antidepressants)

Antiepileptic carbamazepine was detected most frequently and in highest concentration in wastewater (up to 6.3 μg/L) (Ternes 1998) and at lesser concentrations in other media (Heberer 2002). Carbamazepine was found in all effluent samples of the Canadian STP at concentration up to 2.3 μg/L. This substance was reported to be present in all samples of German river Elbe and streams (Wiegel et al. 2004), exceeding 1 μg/L in other surface waters (Ternes 1998; Heberer 2002) and also occurred in groundwater (Sacher et al. 2001). Carbamazepine was also reported at average levels of 20.9 ng/mg solids of STP. Diazepam was noted in 8 out of 20 treatment plants in Germany at relatively low concentrations of up to 0.04 μg/L (Ternes 1998), whereas in Belgium it was recorded at concentration up to 0.66 μg/L (van derVen et al. 2004). The antidepressant fluoxetine was also recorded in Canadian effluent samples, and in US streams, median concentrations of 0.012 μg/L were estimated (Kolpin et al. 2002). In addition to these, an antiepileptic drug, primidone (0.6 μg/L), was also identified in sewage (Heberer 2002).

1.5.4.1 Mode of Action

Antiepileptic drugs decrease the overall neuronal activity. This can be achieved either by blocking voltage-dependent sodium channels of excitatory neurons (e.g. carbamazepine) or by enhancing inhibitory effects of the GABA neurotransmitter by binding on an exact site in the gamma subunit of the corresponding receptor (e.g. diazepam, member of benzodiazepine family). The uptake of serotonin is inhibited by a very common antidepressant, fluoxetine. It is a neurotransmitter that has to do with hormonal and neuronal mechanisms, and it is vital for sexual behaviour and food intake. Fluoxetine, sertraline, norfluoxetine and desmethylsertraline have been discovered in fish sampled from the wild in the USA and therefore reflect a bioaccumulation potential (Brooks et al. 2005).

1.5.5 Various Other Compounds

Effluents of the sewage treatment plants and surface waters which have been contaminated by drugs are comprised of caffeine and cotinine (a nicotine metabolite).

In the USA, caffeine was found in streams at high levels of 6.0 μg/L (median 0.1 μg/L) (Kolpin et al. 2002) which can serve as an anthropogenic marker in aquatic systems as a result of its ubiquity in surface water, in seawater (Wiegel et al. 2004) and also in groundwater. Cimetidine and ranitidine (antacids) were estimated to occur at concentrations of 0.58 and 0.01 μg/L, respectively, in streams in the USA (Kolpin et al. 2002). Iopamidol has been detected in municipal wastewater at very high concentrations (15 μg/L), in surface water (0.49 μg/L) and in groundwater.

The antidiabetic compound metformin was observed in 5 % of stream water samples with estimated levels of 0.11 μg/L (Kolpin et al. 2002). Bronchodilators (β2-sympathomimetics terbutaline and salbutamol) were also detected in sewage not exceeding 0.2 μg/L (Ternes 1998).

1.5.5.1 Mode of Action

Cimetidine and ranitidine are compounds, which act by hindering the histamine receptor type 2 in the gastric system, thus inhibiting the acid secretion (antacid). These drugs are for the treatment of gastric ulcer. Metformin is an antidiabetic agent, whose mechanisms of actions have not been fully studied. It has been reported that this drug acts by increasing the cellular use of glucose and inhibiting the gluconeogenesis. Metformin acts on insulin receptor by direct stimulation of the insulin receptor or indirectly through inhibition of tyrosine phosphatase (Holland et al. 2004).

1.5.6 Steroidal Hormones

Steroidal hormones have been reported in wastewater and surface waters in a number of countries in Europe, Canada, the USA, Japan, Brazil, etc. A study in the USA showed that the average oestrogen concentration was 73 ng/L and levels of mestranol were 74 ng/L (Kolpin et al. 2002). They were detectable in 16 and 10 % of the streams sampled. Typical wastewater effluent concentrations are 0.5 ng/L and they are even lower in surface water.

1.6 Effects of Xenobiotics on Ecosystem

Every year, more than 13 million deaths and 24 % of world diseases are said to be as a result of environmental pollutants/exposures which can be avoided. Today, detectable levels of pharmaceutical preparations either as parent drug or metabolite are present in foodstuffs and water, i.e. both rivers and seas (Bonjoko 2014). Medications for humans and animals have severe consequences extending far beyond the traditional objectives of conventional medical care. The healthcare industry is the major source of active pharmaceutical ingredients (API) from medications, residues of which could lead to environmental pollution.

1.6.1 Effects on Aquatic Ecosystem

Aquatic organisms are significant biological indicators of pollution. Fent et al. (2006) conducted a comprehensive study on the occurrence; end result of pharmaceuticals in the aquatic environment, discussed potential mechanisms of action based on knowledge from mammalian studies and described the acute and chronic ecotoxicological effects on organisms. Pharmaceuticals are most often released back into the environment either in their original form or as metabolites. In humans, the main pathway is ingestion following excretion and disposal via wastewater. Municipal wastewater is the largest source of human pharmaceuticals. Hospital wastewater, wastewater from manufacturers and landfill leachates may contain significant concentrations of pharmaceuticals. Pharmaceuticals that are nondegradable in the sewage treatment plant (STP) are being released into treated effluents resulting in the contamination of rivers, lakes, estuaries and, rarely, groundwater and eventually drinking water. There is also likelihood of contamination when sewage is applied in agriculture. In addition, drugs meant for animals enter the waterways during surface application for agriculture purposes and runoff and also via direct application in fish farming. Pharmaceuticals of environmental significance oftentimes have high production volume in addition to environmental persistence and biological activity, especially after long-term exposure.

In recent studies, it has been observed that the increasing amounts of pharmaceuticals found in surface waters worldwide have raised concerns especially with respect to their effects on the aquatic flora and fauna. It would therefore be a huge task to initiate a strategy for prioritizing drugs on which to focus the most expensive environmental research efforts on. Among aquatic organisms, fish most often share drug targets with humans. Not much is known about the long-term effect of drugs in aquatic organisms. Diclofenac influences the expression of genes in fish and organ histology when exposed to a concentration of 1 μg/L of this drug (Cuklev et al. 2012). A study in India on surface water from 27 locations of the Kaveri velar and Tami rapani rivers in southern India revealed the presence of a number of nonsteroidal anti-inflammatory drugs (NSAIDs): naproxen, ibuprofen, diclofenac, acetylsalicylic acid and ketoprofen. This situation poses risks of direct toxicity to all consumers of the water (Shanmugan et al. 2013). Another case, likewise, effluents from a treatment plant in Hyderabad, India, was observed to be the cause of deleterious effects on water organisms. An embryo toxicity test that was carried out observed that as little as 0.2 % of the effluent reduced tadpole growth by 40 %; however, zebra fish (*Danio rerio*) growth was not impeded. Although the study focused on fish, it also increased knowledge about how aquatic vertebrates are possibly affected by effluent exposures, which substances in the effluent are causing the toxic effects and their threshold dilutions (Shanmugan et al. 2013).

Streams and rivers have been identified to be exposed to combinations of different drugs. Antidiabetic and antihistamine diphenhydramines were observed to cause significant disruption to the biofilm community which is important to the ecosystem. Biofilms are aggregates of microorganisms in which cells that are frequently embedded within a self-produced matrix of extracellular polymeric substances

(EPS) adhere to each other and or to a surface. Biofilms serve as the important food source for invertebrates that in turn feed larger animals like fish. The effects of diphenylamines on biofilm could therefore have repercussion for animals in stream food web such as insects and fish (Rosi-Marshall 2013). The use of antidepressants disrupts the aquatic equilibrium by activating early spawning in some shellfish. Furthermore, propranolol and fluoxetine were observed to have deleterious effects on zooplankton and benthic organisms (Hoffman et al. 2005). Factors such as cellular recognition of specific or non-specific attachment sites, nutritional cues or the exposure of planktonic cells to subinhibitory concentration of antibiotics lead to the formation of biofilms by microbes (Hoffman et al. 2005; Karatan and Watrick 2009). Masculinization (imposex) had been witnessed in female marine snails exposed to tributyltin (TBT). The dog whelk (*Nucella lapillus*), 'a species of predatory sea snail', is particularly sensitive, and imposex has resulted in decline or extinction of local populations worldwide, including coastal areas all over Europe and the North Sea.

DDE (dichlorodiphenyldichloroethylene)-induced eggshell thinning in birds is probably the best example of reproductive impairment causing several population declines in a number of raptor species in Europe and North America. Gradual exposure to the DDT complex (dichlorodiphenyltrichloroethane) has been linked to ovotestis in male western gulls. EDCs (endocrine disruptors) have negatively affected a variety of fish species exposed to effluents causing reproductive problems. Turtles have also been affected in a similar manner (Cleuvers 2003; Le Page et al. 2011). Triclosan (TCS) is a broad-spectrum antimicrobial compound that is contained in most of the cleaning products for the prevention of bacterial, fungal and mildew growth. Triclosan enters into water streams from domestic wastewater, leaking sewerage and sewage overflows. The continuous use of these antibiotics leads to the emergence of resistant bacteria that could diminish the usefulness of important antibiotics (Drury et al. 2013).

1.6.2 Effects on Animals

More commonly observed effects of EDC are impaired reproduction and development in aquatic animals (Kid et al. 2007). A number of brain targets for EDC present in environmentally relevant concentrations in surface waters had been identified from recent surveys. In mammals, field studies on Baltic grey and ringed seals and Wadden Sea harbour seals revealed that reproduction and immune function were impaired by PCBs (polychlorinated biphenyls). Other mammals in the food chain that have the likelihood of being affected include the polar bear, rabbit and guinea pig. In Florida, due to a pesticide spill, alligators were found to have inhibited genital developments. Furthermore, the oestrogenic and androgenic effects observed have been linked to experimental studies with alligator eggs to the DDT complex.

1.6.3 Effects of Plants

With the growing influence of herbal drugs worldwide, botanical plants with pharmacological properties should be cautiously handled in order not to contaminate crops, vegetables and surface water. A common herb which may contaminate the ecosystem is marijuana with the potential ability to interfere with the biological system of aquatic organisms. In addition, herbs like St. John's wort were noted to cause modulation of cytochrome p450 and may interfere with prescribed therapeutic agents (Guengerich 1997). *Aristolochia* plants are commonly used in traditional herbal preparation as health supplements and remedies for various health problems including weight loss, menstrual symptoms and rheumatism. In the 1990s, epidemiological studies revealed AA exposure was associated with a high risk of nephrotoxicity and upper urinary tract urothelial cell carcinoma (UTUC) (Grollman et al. 2007; Debelle et al. 2008) caused by the ability of AA to bind DNA, forming DNA adduct (Schmeiser et al. 1998). These findings eventually resulted in the ban on *Aristolochia*-containing herbal preparations in Europe and North America since 2001 and in Asia since 2003 (Debelle et al. 2008). Currently, AA is classified in the International Agency for Research on Cancer (IARC) monograph as a group 1 human carcinogen (IARC 2012). There is the likelihood that AA may contaminate surface water, grain and vegetables during the processing of *Aristolochia*-containing herbs and the disposal of its waste. TP 53 mutation signature in urothelial tumours and the existence of aristolactam-DNA adducts in the renal cortex are defined in the course of research as a robust biomarker of exposure to this potent nephrotoxin and human carcinogen (Moriya et al. 2014).

1.6.3.1 Pesticides

Ninety percent of pesticides currently in use are synthetic, but in the past 20 years, there had been conscious attempts to develop safe and environmentally friendly pesticides. Organic or natural pesticides have received the most acclaim and certain have the endorsement of environmentalists. Pesticides such as fungicides, herbicides and rodenticides can be very helpful in the sense that they protect man's health by killing germs, animals or plants that can hurt us. On the other hand, a good number of pesticides can be injurious to human and animals. The proper disposing of pesticides is very vital for the protection of the environment. Biologically based pesticides are becoming more popular as they are safer than traditional pesticides. They come in the form of pheromones and microbial pesticides. To insects and rodents, pesticides are inherently toxic. Organophosphate and organochlorine insecticides (synthetic pesticides) have been linked to a wide range of ailments from cancer to neurological disorders and lung irritations in humans. A diversity of pesticides like mineral oil, malathion, sulphur dimethylamine and many others are used to control fungi and insects on wheat and cereals. Chlorinated hydrocarbons present in synthetic pesticides such as methoxychlor, endosulfan and captain accumulate in fatty tissue because it is not completely filtered from the system.

1.6.4 Effects on Humans

The possible exposure pathway of endocrine disruptors in humans includes direct exposure at the workplace and via consumer products such as food, certain plastic, paints, detergents and cosmetics as well as indirect exposure via the environment, viz. air, water and soil. Apart from the drug DES (synthetic oestrogens), environmental oestrogens were not proven to cause human health problems. Lead is regarded as being hepatotoxic, while cadmium is a well-known nephrotoxic agent. Health effects of pesticides are irritation to the eye, nose and throat, injury to the central nervous system and kidney and augmented risk of cancer. Symptoms of pesticide toxicity include nausea, muscular weakness, headache and dizziness, whereas chronic exposure to certain pesticides could result in liver, kidney, endocrine and nervous system damage. Exposure to elevated levels of cyclodiene pesticides associated with improper use caused various symptoms, including headaches, dizziness, muscle twitching, weakness, tingling sensation and nausea. It is assumed that cyclodienes might cause long-term damage to the liver and the central nervous system as well as a heightened risk of cancer.

Steroid receptors for oestrogens and androgen functions of the brain and the cardiovascular, the skeletal and the urogenital system are regulated by these hormones and can therefore be affected by EDCs. EDCs have the potential to cause reduced quality of semen and low sperm counts, low ejaculate volume and high number of abnormal spermatozoa motility. Other effects may include testicular cancer and malformed reproductive tissue, viz. undescended testes, small penis size, prostate disease and other unrecognized abnormalities of male reproductive tissues. Bisphenol A, a component used for plastic products, binds to the local anaesthetic receptor site to block the human cardiac sodium channel. There are currently putative links between EDC and some female diseases including breast and reproductive organ tissue cancers, fibrocystic disease of the breasts, polycystic ovarian syndrome, endometriosis, uterine fibroid and pelvic inflammatory diseases. Phthalates, most often used in cosmetics like nail polish, are reported to affect the endocrine system and are being investigated for a link with infertility in women. EDCs have been associated to impaired behaviour, mental, immune and thyroid functions in developing children. Others include precocious puberty, osteoporosis, foetal growth and obesity (Meeker 2012). Children are most prone to environmental contaminants from foodstuff to drug and plastic toys. They are similarly quite vulnerable to poisoning from unprescribed medications.

1.6.4.1 Autoimmune Diseases

Environmental exposures play a role in the development and/or the exacerbation of autoimmune diseases (Ritz 2010). Autoimmune diseases collectively afflict approximately 24.5 million Americans with women disproportionally affected. Autoimmune diseases such as rheumatoid arthritis (RA), systemic sclerosis (SSc), systematic lupus erythematosis (SLE) and anti-neutrophil cytoplasmic antibody (ANCA)-related vasculitis, solvent exposure and the development of SSc and smoking and the development of seropositive RA, and an inverse relationship between

ultraviolet radiation exposure and the risk of development of multiple sclerosis (MS) can be caused. The mechanisms by which environmental factors alter basic biological processes to induce autoimmune diseases continue to be examined but remain largely unknown. Several studies point to many mechanisms likely involved in environmental exposure-based autoimmunity and include a role for xenobiotics in the activation of Toll-like receptors (TLRs), B-cell activation, impairment of T helper 17 (Th 17) and T-regulatory (T-reg) cell immune function, modifications of self-antigens and alteration of DNA methylation profiles. Despite growing advances in the field, knowledge of the interactive roles of the environment and genetics in the autoimmune process is still lacking, and additional progress is needed on many fronts.

1.7 Other Forms of Environmental Pollutants

Nickel, arsenic, chromium and lead are well-known environmental toxicants. Many household products like insecticides, paints, cosmetics, cleaning fluids and nanomaterial-based items are known to contain some of these toxicants. Even though they may not be directly toxic, their interaction with cellular organelles results in cancer. Many household products (oven and drain cleaners, laundry powder, floor polish, paint and pesticides) are potentially dangerous substances. Arts and craft supplies and gardening products can be hazardous. Many household products can be harmful to kids and pets and end up in the ecosystem if not properly disposed. Exposure via inhalation, swallowing or absorption through the skin is a potential killer. Recent evidence had shown that natural health products (NHPs) therapies are gradually more suggested by health providers, including conventional physicians leading to increased consumption of vitamins and many herbal agents worldwide. The WHO (World Health Organization) reports that the current annual need for medicinal plants is approximately US $14 billion, and it is estimated to likely increase to about $5 trillion by 2050. Cultivators of herbs for medicinal uses are usually ignorant of the WHO regulations, and these products may be infected with banned pesticides and microbial agents like fungi, heavy metals and chemical toxins which may cause unfavourable outcomes such as sensorineural defects, congenital paralysis and liver and kidney damage. In addition Wong et al. (1993) also reported concentration of heavy metals such as cadmium, cobalt, copper, iron, manganese, nickel lead, zinc and mercury in Chinese herbal drugs. Chloramines and chlorine dioxides are well-known disinfection methods to eradicate harmful microorganisms. Chlorine reacts with organic compounds in water to form potentially harmful chemical by-products. These by-products include triethylin, trihalomethanes (THMs) and haloacetic acids (HAAs) are carcinogenic in large quantities and are regulated in the USA by the Environmental Protection Agency. Chloroform, dichloroacetic acid (DCA) and trichloroacetic acid (TCA) which are known liver and kidney carcinogens are by-products of chlorine disinfection found in drinking water. Trihalomethanes, viz. chloroform, bromo-dichloromethane, chlorobromomethane and bromoform, are regulated organic contaminants in drinking

water. Methylation in the promoter region of the c-myc gene was reduced by the trihalomethanes, a process consistent with carcinogenic activities.

1.8 Conclusion

With population increase and urbanization, there is high likelihood of xenobiotic contamination in our food and water. Right from our daily care products to agricultural uses, the existence of harmful xenobiotics has been detected. Even though there are a number of sewage treatment and detection methods, xenobiotics is fast becoming a peril to our ecosystem as over long term there is bound to be repercussions. Long-term effects are autoimmune disorders, liver and kidney damage, cardiac problems and eventually cancer as a result of prolonged consumption of these pollutants in food or drinks. It is therefore a great challenge to the environment health researchers to address this issue. Research is being carried out on antibiotic resistance in sewage as the current trend will lead to a worldwide disaster. The earlier remedies or preventive methods are established, the better it is for the natural ecosystem.

Acknowledgement The author Katheem Kiyasudeen acknowledges University Sains Malaysia (USM) for funding and research facilities via RUI grant (Grant Number: 1001/PTEKIND/811254) and USM fellowship-2015 award for academic support'.

References

Bjorkman D (1998) Nonsteroidal anti-inflammatory drug associated toxicity of the liver, lower gastrointestinal tract, and esophagus. Am J Med 105(5, Suppl. 1):7S–21S

Bonjoko B (2014) Environmental pharmacology: an overview. In: Pharmacology and therapeutics (Monograph on the internet). Intech, pp 133–178. Available from: http://www.intechopen.com/books/pharmacology-andtherapeutics/environmental-pharmacology-an-overview

Brooks BW, Chambliss CK, Stanley JK et al (2005) Determination of select antidepressants in fish from an effluent-dominated stream. Environ Toxicol Chem 24(2):464–469

Cajaraville MP, Cancio M, Ibabe A, Orbea A (2003) Peroxisome proliferation as a biomarker in environmental pollution assessment. Microsc Res Tech 61:191–202

Cleuvers M (2003) Aquatic ecotoxicity of pharmaceuticals including the assessment of combination effects. Toxicol Lett 142(3):185–194

Cuklev F, Fick J, Cvijovic M et al (2012) Does ketoprofen or diclofenac pose the lowest risk to fish? J Hazard Mater 229–230:100–106

Debelle FD, Wanherghem JL, Nortier JL (2008) Aristolochic acid nephropathy: a worldwide problem. Kidney Int 74:154–169

Doggrell SA (1990) The membrane stabilizing and beta1- adrenoceptor blocking activity of (+) – and (−) -propranolol on the rat left atria. Gen Pharmacol Vasc Sci 21(5):677–680

Drury R, Scott J, Rosi – Marshall EJ, Kelly JJ (2013) Triclosan exposure increases triclosan resistance and influences taxonomic composition of benthic bacterial communities. Environ Sci Technol 47(15):8923–8930

Fent K, Weston AA, Caminada D (2006) Ecotoxicology of human pharmaceuticals. Aquat Toxicol 76:122–159

Fetzner S (2002) Biodegradation of xenobiotics. In Encyclopedia of Life Support Systems (EOLSS) Publishers, developed under the Auspices of the UNESCO. Biotechnology, Edited by Doelle and Da Silva. EOLSS Oxfor, U.K. p 32

Fick J, Lindberg RH, Tysklind M, Larsson DG (2010) Predicted critical environmental concentrations for 500 pharmaceuticals. Regul Toxicol Pharmacol 58(3):516–523

Garrison AW, Pope JD, Allen FR (1976) Analysis of organic compounds in domestic wastewater. In: Keith CH (ed) Identification and analysis of organic pollutants in water. Ann Arbor Science, Michigan, pp 517–566

Grollman AP, Shibutani S, Moriya M, Muller F, Wu L, Moil U, Swzulai N, Fernandes A, Rosenqiust T, Medeverec Z, Jakovinak BB, Slade N, Turesky RJ, Goodenough AK, Rieger R, Nukelic M, Jelakovic B (2007) Aristolochic acid and the etiology of endemic. (Balkan) nephropathy. Proc Natl Acad Sci U S A 104:12129–12134

Gross B, Montgomery-Brown J, Naumann A, Reinhard M (2004) Occurrence and fate of pharmaceuticals and alkylphenol ethoxylate metabolites in an effluent-dominated river and wetland. Environ Toxicol Chem 23(9):2074–2083

Guengerich FP (1997) Role of cytochrome p450 enzymes in drug – drug interaction. Adv Pharmacol 47:7–35

Gunnarsson L, Kristiannsson E, Rutgersson C, Sturve J, Fick J, Forlin L, Larsson DGJ (2009) Pharmaceutical industry effluent diluted 1:500 affects global gene expression, cytochrome 1A activity and plasma phosphate in fish. Environ Toxicol Chem 28(12):2639–2647

Heberer T (2002) Occurrence, fate, and removal of pharmaceutical residues in the aquatic environment: a review of recent research data. Toxicol Lett 131(1/2):5–17

Hoffman LR, D' Argenio DA, MacCoss MJ et al (2005) Aminoglycoside antibiotics induce bacterial biofilm formation. Nature 436(7054):1171–1175

Holland W, Morrison T, Chang Y et al (2004) Metformin (glucophage) inhibits tyrosine phosphatase activity to stimulate the insulin receptor tyrosine kinase. Biochem Pharmacol 67(11):2081–2091

IARC (2012) IARC working group on the evaluation of carcinogenic risks to humans; pharmeceuticals. Volume 100A. A review of human carcinogens. IARC Monogr Eval Carcinog Risks Num 100:101–401

Jain RK, Kapur M, Labana S, Lal B, Sarma PM et al (2005) Microbial diversity: application of micro-organisms for the biodegradation of xenobiotics. Curr Sci 89(1):101–112

Jones OAH, Voulvoulis N, Lester JN (2001) Human pharmaceuticals in the aquatic environment. Environ Technol 22:1383–1394

Karatan E, Watrick P (2009) Signals, regulatory networks and materials that build and break bacterial biofilms. Microbiol Mol Biol Rev 73(2):310–347

Kid KA, Blanchfield PJ, Mills KH et al (2007) Collapse of a fish population after exposure to a synthetic estrogen. Proc Natl Acad Sci U S A 104(21):8897–8901

Kolpin DW, Furlong ET, Meyer MT et al (2002) Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams 1999–2000: a national reconnaissance. Environ Sci Technol 36(6):1202–1211

Landrum PF, Robbins JA (1990) Bioavailability of sediment-associated contaminants to benthic invertebrates. In: Baudo R, Giesy JP, Muntau H (eds) Sediments: chemistry and toxicity of in-place pollutants. Lewis Publishers Inc, Chelsea

Le Page Y, Vosges M, Servil A, Brown F, Kah O (2011) Neuroendocrine effects of endocrine disruptors in teleost fish. J Toxicol Environ Health B Crit Rev 14(5–7):370–386

Lee II H (1992) Models, muddles, and mud: predicting bioaccumulation of sediment-associated pollutants. In: Burton Jr. GA (ed) Sediment toxicity assessment. Chelsea

Maenpaa KA (2007) The toxicity of xenobiotics in an aquatic environment: connecting body residues with adverse effects. PhD Dissertation, University of Joensuu, Finland

Meeker JD (2012) Expensive to environmental endocrine disruptions and child development. Arch Pediatr Adolesc Med 166(10):952–958

Moriya M, Slade N, Brder B, Medverec Z et al (2014) TP53 mutational signature for aristolochic acid: an environmental carcinogen. Int J Cancer 129:1532–1536
Newman MC (1998) Fundamentals of ecotoxicology. Sleeping Bear/Ann Arbor Press, Chelsea
Reineke W, Knackmuss HJ (1988) Microbial degradation of haloaromatics. Annu Rev Microbiol 42:263–287
Richardson ML, Bowron JM (1985) The fate of pharmaceutical chemicals in the aquatic environment. J Pharm Pharmacol 37(1):1–12
Ritz SA (2010) Air pollution as a potential contributor to the 'epidemic' of autoimmune disease. Med Hypothesis 74(1):110–117
Rosi-Marshall E (2013) Streams stressed by pharmaceutical pollution. www. Environmental change. nd. edu/events/2 Last visited 10-08-2013
Sacher F, Lange FT, Brauch HJ, Blankenhorn I (2001) Pharmaceuticals in groundwaters: analytical methods and results of a monitoring program in Baden-Wurttemberg, Germany. J Chromatogr A 938(1/2):199–210
Schmeiser HH, Shoepe KB, Wiessler M (1998) DNA adduct formation of aristolochic acid I and II in vitro and in vivo. Carcinogenesis 9:297–303
Shanmugan G, Sampath S, Selvaraj KK et al (2013) Non-steroidal anti inflammatory drugs in Indian rivers. Environ Sci Pollut Res 21(2):921–931
Sikandar A, Shehzadi K, Arshad Q, Munir K (2013) Phytoremediation: an analytical technique for the assessment of biodegradation of organic xenobiotic pollutants: a review. Int J Sci Res 4(2):2250–2253
Streit B (1992) Bioaccumulation processes in ecosystems. Experientia 48:955–970
Ternes TA (1998) Occurrence of drugs in German sewage treatment plants and rivers. Water Res 32(11):3245–3260
van derVen K, Van Dongen W, Maes BUW et al (2004) Determination of diazepam in aquatic samples by capillary liquid chromatography–electrospray tandem mass spectrometry. Chemosphere 57(8):967–973
Wiegel S, Aulinger A, Brockmeyer R et al (2004) Pharmaceuticals in the river Elbe and its tributaries. Chemosphere 57(2):107–126
Wong MK, Tan P, Wee YC (1993) Heavy metals in some Chinese herbal plants. Biol Trace Elem Res 36(2):135–142