Chapter 5

Environmental Pharmacology – An Overview

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Additional information is available at the end of the chapter

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1. Introduction

Pharmacology is the science that studies the physiological and biological effects of exogenous substances which are not part of the internal milieu of a living organism whether natural or synthetic termed xenobiotics (drugs, chemicals) on the cells, tissues, or organs of the organisms. There are many specialized areas of pharmacology and these include clinical pharmacology; which deals with the application of pharmacological principles and methods in the medical clinic with the focus on patient care and outcomes, neuro-pharmacology; which deals with effects of medication on central and peripheral nervous system function, psychopharmacology; which observes the effect of medication on the changed behaviours of the mind and body and how molecular events are manifested in a measurable behaviourable form. Other areas are pharmacodynamics; the chemical effect on the body, pharmacogenetics; the genetic variation that gives rise to differing response to drug, and the related area of pharmacogenomics, which is the application of genome technologies and the influence of the whole human genome on drug response, toxicology; which studies the harmful effect of drugs or chemicals and their molecular targets and characterization, pharmacognosy; the study of medicinal substances of biological origin, pharmacokinetics; that deals with the effect of the body on chemical half life and lastly environmental pharmacology which can be defined as the effect of pharmaceuticals and house care products on the environment and the ecosystem (Halling-Sorensen et al 1998). Environmental pharmacology is a relatively new and emerging specialty of pharmacology. It involves the study of gene-environment interaction, drug-environment interaction and toxin-environment interaction. It is important to emphasize at this stage that the different terms used interchangeable with environmental pharmacology include ecopharmacology, and pharmacoenvironmentology, ecotoxicology. However, a close similarity exists between environmental pharmacology and ecotoxicology. Environmental pharmacology entails the study of environmental science, medicine, ecology, genetics and chemistry.

The impact of pharmaceuticals on the ecosystem has significance public health implications. The demand for more pharmaceuticals relative to world's population growth may place the public at risk though the destruction of species. The entry of chemicals and drugs into the aquatic ecosystem is of a serious concern and empirical evidences are making these concerns more compelling. In addition, the production of illegal drugs pollutes drinking waters supply by releasing possible carcinogens (Ruhoy and Daughton 2008). All these factors necessitate the need for substances that are more biodegradable for the manufacture of drugs by pharmaceutical companies. However, environmental contamination by drugs may or may not lead to toxic effect on the ecosystem but usually there can be modifying effects. (Daughton and Ternes 1999)

1.1. Historical perspectives

In recent years, human pharmaceuticals from numerous therapeutic classes have increasingly been detected in the environment, typically at ng/l to low μg/l in surface water (Holm et al 2008). Another notable observation was the traces of narcotics like cocaine in River Thames (Goswani and Orr 2005). In addition, illegal cultivation of marijuana in bushes close to surface water with potential effect on the ecosystem is also a source of concern. The observation in 1997 of the decline in the population of the Asian white- backed vulture (Gyp) and the Indian vulture nesting in Keoladeo Natural Park in North Western India prompted the Indian Government to ban the drug 'diclofenac'. The vulture population drastically reduced over the years from 150 in 1997 to 25 in 2010. It was observed that they die after feeding on cattle treated with diclofenac. Diclofenac sodium is a non steroidal anti -inflammatory (NSAID) pain killer used by veterinary doctors to treat cattle. Because of lack of proper detoxification pathway for diclofenac in vultures, it's ingestion leads to visceral gout and subsequent renal failure and death when they feed on the carcasses of animals treated with the drug (Oaks et al 2004).An alarming decline in the number of vultures poses the threat of outbreak of epidemics because of increase in the population of undecayed carcasses and feral dogs which pose a range of disease threats such as rabies in India (Brakash et al 2003).

Effects of some drugs on aquatic organisms have been investigated in acute toxicity assays However, the chronic toxicity and potential subtle effects are only marginally known (Fent et al 2006). Environmental contamination by pharmaceuticals is not restricted to developing countries but it is a worldwide phenomenon. This underscores the importance of this emerging field of pharmacology. A study in the United States by the Geological Survey Department found traces of many different drugs and personal care products including steroids, insect repellants and phthalates in the American water supply. Although the concentrations were in traces, the effect of chronic exposure can be unpredictable (Palla va Bagla 2004). The production of bulk drugs has also been recently identified as an important source for environmental pollution with active pharmaceutical ingredients in certain locations (Gunnarson et al 2009, Fick et al 2010).A growing number of pharmaceutical residues are also found in surface water worldwide, raising concerns about their effects on the aquatic organism and posing a major challenge to developing rational strategy for prioritizing drugs on which to focus the most extensive environmental research efforts (Fick et al 2010). Traces of drug residues may pose

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risk to aquatic life as depicted by various studies (Daughton and Terres 1997, Cleavers 2003, Boxall et al 2004, Kidd et al 2007). There is equally concern to human health sequel to the exposure to contaminated drinking water (Daughton 2004, 2008).

2. Sources and fate of pharmaceutical and house care products in the environment

The potential routes of entry of pharmaceutical and house hold care products in the environment include :

i. patients' excretion either as a parent compound or metabolites, via the sewer system

ii. direct release into the waste water system from manufacturing, hospitals or disposed via toilets and sinks

iii. terrestrial depositions for example via sludge application to land, leaching from solid waste landfills or irrigation with treated and untreated waste water. It is generally accepted that excretion of pharmaceuticals after human and veterinary therapeutic use dominates the global input of pharmaceuticals into the environment. Manufacturing effluent discharges and the disposal of unused drugs make a relatively small contribution to the overall environmental drug load. In addition, localized increased concentrations of drugs can occur adjacent to discharges from hospitals.

iv. Non pharmaceutical industrial sources, for example plastic products manufacturers are potential sources for the release of bisphenol A; used in the manufacturing process and known to have pharmacological effects on man and aquatic animals. Another pollutant from many household products is phthalates.

v. Overflow of agricultural run off may contain herbicides, pesticides and fertilizers and pose a potential danger to the ecosystem.

vi. Aging infrastructure also promotes the release of pharmaceuticals to the environment. Even when waste water makes it to sewage treatment facilities, they are not equipped to remove pharmaceuticals. As a result, our steams and rivers are exposed to a cocktail of synthetic compounds from stimulants and antibiotics to analgesics and anti histamines.

vii. Another important source of pharmaceuticals in the environment are drugs destined for plant health. For example, plant parasitic nematodes cause global crop losses of about $125billion annually. Current chemicals used to control these pests have been withdrawn due to their environmental toxicity. This necessitated companies like Bayer Crop Science to reinforce research in this respect in order to come up with a suitable and safer alternative product.

viii. There has been little consideration for herbal preparations and their interaction with the environment, since they possess pharmacological properties. A recent example

can be found in aristolochic acid, a carcinogen, mutagen and nephrotoxin commonly found in *Aristolochiacea* family of plants including *Aristolochia* (Birthworth) and *Asarum* (wild ginger) which are commonly used in Chinese herbal medicine (Barceloux 2008, Henrich et al 2009,Gluhovschi et al 2011). Aristolochic acid I is the most abundant of the aristolochic acids and it is found in almost all aristolochia species. Aristolochic acids are often accompanied by arisolactams which has been implicated as the causative agent of Balkan endemic nephropathy, Chinese herbs nephropathy and urothelial cancer.

2.1. Pharmaceutical active compounds (PhACs)

Pharmaceutical active compounds (PhACs) are those pharmaceuticals that have by one route or another entered the environment as the parent compound or as pharmacologically active metabolites. For many years, PhACs was not given any meaningful attention due to the fact that environmental researchers concentrated on the well known environmentally dangerous chemicals that are largely used in agriculture and industry. PhACs have not until recently been seen as potentially toxic because regulations associated with pharmaceuticals are typically overseen by drug related organizations which have limited experience with environmental issues (Jones et al 2001).

The list of common PhACs found in the environment includes

i. Analgesics with anti inflammatory and anti pyretic capabilities viz acataminophine, acetylsalicylic acid, diclofenac, codein and Ibuprofen

ii. Antibiotics: macrolide antibiotics, sulfonamide fluoroquinolones, chloramphenicol, tylosin, trimethoprin, erythromycin, lincomycin, sulfamethoxazole and trimethoprin.

iii. Anticonvulsant: carbamazepine, primidone.

iv. Beta – blockers: metoprolol, propanolol, betaxolol, bisoprolol, nadolol

v. X ray media: 10 promide, 10 pamidol, 10 hexol and diatrizoate.

vi. Steroid and hormonal preparation: 17 α ethinyl estradiol, mestrennol and 19-noresthisterone

vii. Miscellanous: household products, pesticides veterinary drugs and insecticides.

2.1.1. Fate in the environment

Once PhACs enters the environment, they suffer one of three fates which include:

i. Biodegradation into carbon dioxide and water

ii. Undergo some form of degradation to form metabolites

iii. Persist in the environment unmodified. The amount of the compound that is broken down depends on several factors such as bioavailability and compound structure among others.

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2.2. Biodegradation of xenobiotics

Biodegradation is the complete breakdown of the complex and toxic contaminates to non-toxic simple elements by the action of microbes. Hence, these contaminants act as the microbial food substrate. Biodegradation, in general can be considered as a series of steps of biological degradation or pathway that ultimately result in the oxidation of the compound which most often results in the generation of energy while xenobiotics in the human body are removed by a process called xenobiotic metabolism, in which these compounds are degraded by the liver enzymes such as Cytochrome P_{450} which activate the xenobiotics by the process of oxidation, or hydration, reduction or hydration followed by conjugation with glucuronic acid, sulphuric acid or glutathione, and the compound conjugates are excreted by urination, exhalation, sweating and defeacation. The xenobiotics in the environment are degraded by the microbes. Microbes have the capacity to degrade all naturally occurring compounds by the principle of microbial infallibility proposed by Alexander in 1985. Microbes can degrade many of the xenobiotic compounds, but not all. The compounds that resist biodegradation and persist in the environment are called "recalcitrant or Environmental persistent pharmaceutical pollutants (EPPP).

For complete biodegradation, oxidation of parent compound occurs to form carbon dioxide and water. Each step in the degradation pathway is catalyzed by a specific enzyme produced by the degrading cell. Degradation of some xenobiotics depends on the presence of a specific compound, which includes the required enzymes. These enzymes are metabolized to provide both energy and reducing equivalent for the degradation of xenobiotics compounds. Example of such enzymes are the oxygenases; a group of enzymes that catalyses the reactions that transforms the hydrophobic nature of the organic compound to water soluble forms which can be broken down by a larger number of other micro organisms. The oxygenases are of two main classes; mono-oxygenases and dioxygenases. These enzymes participate in the oxidative metabolism of a wide variety of chemicals of pharmaceutical, agricultural and environmental significance. Some of the most widely recognized substrate for this class of enzymes are the aliphatic and aromatic hydrocarbons of both endobiotic and xenobiotic sources. Monoxygenases are a class of enzymes that insert one atom of the oxygen molecule into the substrate; the other atom becomes reduced to water. They are also more complex and can catalyze several different types of oxygen atom insertion reactions. Since they can oxidize more than one substrate, they are called mixed functions oxidizers or oxidases. Also, since one of the main substrates gets hydrolysed they are also called hydroxylases. The general stoichiometry of the is reaction is as follows:

$$R\text{-}H + NAD(P)H + 0_2 \rightarrow R - OH + NAD(P) + H_20$$

Dioxygenases incorporate both atoms of the oxygen molecule into substrate and are crucial in initiating the decomposition of a variety of chlorinated and nitro-aromatic compounds as well as non-substituted polycyclic aromatic hydrocarbons. Many of these compounds are first degraded to catechol protocatechuate by oxygenases (dioxygenases and monoxygenases).The intermediates are metabolized by ring cleavage type of dioxygenases to either beta-keto adipate or 2keto-4-hydroxy valerate. These intermediates then enter the TCA cycle. When the organism evolves to start tolerating the xenobiotic compound, it can lead to the phenomenon

called 'resistance'. An example is the resistance of the bacteria to certain antibiotics. In addition, some of these substances are resistant to degredation, for example plastics and certain pesticides. However it is understood that microbes have the ability to degrade many of these recalcitrant compounds.

2.2.1. Environmental Pharmaceutical Persistent Pollutants (EPPP)

The term Environmental Pharmaceutical Persistent Pollutants (EPPP) was suggested in the nomination 2010 of Pharmaceutical and Environment as an emerging issue to Strategic Approach to International Chemical Management (SAICM) by the International Society of Doctors for the Environment (ISDE). Pharmaceuticals are synthetic chemicals belonging to a wide group of different chemical families and may also react differently in the environment. There are documented evidences that some pharmaceuticals enter and persist in the environment. (Ruhoy and Daughton 2008, Segura et al 2005) Some are endocrine disruptors, particularly the synthetic hormones (Fick 2009, Snyder et al 2003) some are designed to kill bacteria and viruses and may affect microorganisms and wild life in severe and unexpected ways (Segura et al 2005). Little is known about the possible negative effects and impacts of EPPP in humans and the environment by diffuse and systematic exposure for long periods of time especially during the vulnerable periods of development. As there are thousands of different synthesized chemicals present at the same time in the environment, different interactions may occur and the result of these multiple exposure in human and nature are not sufficiently studied or understood. EPP's are already found in water all over the world. The diffuse exposure might contribute to:

i. Extinction of species and imbalance of sensible ecosystems ; since many EPPS affect the reproductive systems of for example frogs, fish and mussels.

ii. Genetic, developmental, immune and hormonal health effects to humans and other species in the same way as oestrogen- like chemicals.

iii. Development of microbes resistant to antibiotics, as is found in India.

Some pharmaceuticals are degraded to various extents in sewage treatment plants but others leave the plant in active forms. Active residues have been detected in surface water, and they may persist in the environment for long periods of time. Large amounts of antibiotics and other pharmaceuticals have also been found downstream from sewage plants for pharmaceutical industries. EPPs from sewage sludge used as fertilizes can be absorbed by soya, and antibiotics have been found in the leaves. Many EPP's have been detected in drinking water and these include Atenolol (beta blocker) citalopram (anti depresseant drugs Diclofenc (analgesic) Ibuprofen, (analgesic) metoprolol (beta blocker) Neproxen (anti inflammatory) and Trimetoprin (antibiotic) have been found in drinking water of Stockholm, Sweden Fish caught downstream from the sewage plants of Stockholm contained citalopram (antidepressant drug) and propoxyphene (narcotic/anaesthetic) (Daughton 2008, Hernando et al 2006). Several broad – spectrum antibiotics in very high concentrations as well as bacteria resistant to all known antibiotics were found downstream from a sewage plant in India. Also in Indian drinking water, cetrizine (antihistaminic) aprothoxacin (antibiotic), enoxacin (antibiotic) terbinafin

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(antimycotic) and cataboprain (anti depressant drug) were found. Furthermore, up to 14 different pharmaceuticals have been found in the drinking water of big cities around the world. Some of these environmental pharmaceutical chemicals are well known to have serious genotoxic effects in humans. Half life in nature varies depending on the environment (air, water, soil, sludge) but is more than one year for several compounds (Neeman et al 2004, Conroy et al 1999, Sevage et al 2005). Clofibric acid, a metabolite of the lipid lowering agent clofibrate can still be found in surface as well as well-water despite the fact that clofibrate has been withdrawn from use long ago. Concentrations of EPPs can vary from 1ng to 1mg per litre. Serious effects of EPPPS on water living organisms especially on reproductive systems and microbial communities have been observed (Elloriaga et al 2013, Suartz and Perez-coll 2013) Halling- Sorensen 2007, Daughton and Hernes 1999).

3. Effect of xenobiotics on the environment and the ecosystem

More than 13 million deaths every year have been associated with environmental pollutants and as much as 24% of diseases are estimated to be caused by environmental exposures which can be averted. Today, detectable levels of pharmaceutical preparations either as parent drug or metabolite are found in food stuffs, water, i.e both rivers and seas. Although the levels might not be toxic in a single exposure, low dose chronic toxicity should be anticipated. (Jorgenson and Halling-Sorensen 2000).The prescribing and usage of medications for both humans and domestic animals have ramifications extending far beyond the traditional objectives of conventional medical care. The healthcare industry has an environmental footprint that includes the active pharmaceutical ingredients (API) from medications, residues of which can establish themselves as environmental pollutants. Many parallels exist between healthcare and the protection and remediation of the environment, spanning the stages from symptology and diagnosis and treatment (Daughton and Ruhoy 2008).

3.1. Drug – environment interaction (DXE)

Drugs interact with the environment in diverse ways and these include the aquatic system, ground water and surface water, sewage systems, flora and fauna of the ecosystems, causing various modifications including bacterial drug resistance. (Bound and Voulvoulis 2004)

3.1.1. Aquatic system

A growing number of pharmaceuticals are found in surface waters worldwide, raising concerns about their effects on aquatic organisms and it is major challenge to develop a rational strategy for prioritizing drugs on which to focus the most expensive environmental research efforts. Among aquatic organisms, fish most often share drug targets with humans. Very little is known about the long-term effect of drugs in aquatic organisms. A study suggested that anti- depressants like fluoxetine could trigger spawning in some shell fish (Pailla va Balga 2004), thereby disturbing the ecosystem (Jones at al 2001)

An Indian study of effluents from industrial site in which a large number of pharmaceutical companies send their waste water revealed the presence of pharmaceuticals in the treated effluents. In the said study of aquatic rainbow trout (*Oncorhynchus mykiss*) exposed to 0.2% of the effluent for 5 days, induction of hepatic cytochrome P450IA (CYPIA) genes expression as well as enzyme activity were observed. In addition, clinical blood chemistry analysis revealed an increase in plasma phosphate levels which by interpolation in humans, indicates impaired kidney function. In addition, several oxidative stress related genes were found to be induced in the livers, however, no significant changes were observed in antioxidant enzyme activities or in the hepatic glutathione levels. Furthermore, estrogen-regulated genes were slightly up-regulated following the exposure and moderate levels of estriol were detected in the effluent. The pattern of regulated gene may contribute to the identification of mechanism of sub-lethal toxicity as well as illuminate possible causative agent (Gunnarsson et al 2009).

Ketoprofan and diclofenac are non steroidal anti-inflammatory drugs (NSAIDS) often used for similar indications and both are frequently found in surface waters. Diclofenac affects organ histology and gene expression in fish when exposed to a concentration of lμg/l. of this drug (Cuklev et al 2012). In another Indian study, five common non steroidal anti-inflammatory drugs (NSAIDS) namely diclofenac, ketoprofen, naproxen, ibuprofen and acetylsalicylic acid were detected in various concentrations in surface water from 27 locations of the Kaveri vellar and Tami rapani Rivers in southern India. The samples were extracted by solid-phase extraction and analyzed by gas liquid chromatography mass spectrometry (GC-MS). The concentrations of four of the five drugs in this reconnaissance were relatively smaller to those reported elsewhere being of a value of 200ng/l, however, acetylsalicylic acid, the most readily degradable of the drugs, investigated was found at all sites and at considerately higher concentrations of up to 660ng/l, compared to levels reported in European surface waters. The finding of elevated concentrations of acetylsalicylic acid could be as a result of direct discharges of untreated sewage. Therefore, readily degradable pharmaceutical may present larger concern in those regions without consistent sewage treatment. This situation poses risks of direct toxicity to aquatic wildlife and humans consuming the water (Shanmugan et al 2013).

In another case, effluent from a treatment plant; named Patencheru Environment Technology (PETL) which is located in an industrial area just outside Hyderabad in India, was observed to be capable of causing deleterious effects on aquatic vertebrates. In the study,an embryo toxicity test carried out, observed that as little as 0.2% of the effluent, reduced the growth of tadpoles by 40%, however the growth of zebra fish *(Danio rerio)* was not impeded. The median lethal concentration (LC_{50}) of effluent for zebra fish *(Danio rerio)* at 144hr after fertilization varied between 2.7 and 8.1% in different experiments. 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 at what dilutions of effluent are the fish likely to be affected (Shanmugan et al 2013).

3.1.2. Biofilm

Streams and rivers have been known to be exposed to combinations of different drugs. These include commonly prescribed medications like anti- diabetics, anti- histamine diphenylhydr-

http://dx.doi.org/10.5772/57473

amine of which Benachryl is a brand were (Karatan and Watrick 2009) observed to cause significant disruption to the biofilm community which is important to the ecosystem. Biofilms form the slippery coating in stream rocks and are quite vital to stream health where they contribute to water quality by recycling nutrients and organic matter. They are also a major 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). Other effects of drug contamination of the environmental were observed in activities of anti-depressant which could trigger spawning in some shellfish thereby disturbing the ecological balance. Furthermore, propanolol and fluxetine were observed to have deleterious effects on zooplakton and benthic organisms ((Hoffman et al 2005, Rosi-Marshall 2013, NIH 2002).

One of the most important considerations for environmental pharmacology is the impact of drug contaminants on biofilms. 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. Biofilm EPS: also referred to as "slime" is a polymeric conglomeration generally composed of extra cellular DNA proteins and Polysaccharides. Biofilms may form on living or non living surfaces and can be prevalent in natural, industrial or hospital setting (Hall –Stoodley et al 2002, IUPAC 2012, Lear and Lewis 2012). Quite characteristic of biofilms is their ability to grow in the most extreme environments. For example, they can survive in the most extremely hot, briny water of hot springs, acidic and very alkaline waters and frozen glaciers. They can be found on rocks and pebbles at the bottom of most streams or rivers and often form on the surface of stagnant pools of which they are an important components of food chains in rivers and streams which are grazed by the aquatic invertebrates upon which may fish feed. Biofilms are ubiquitous, nearly every species of micro organism, including bacteria and archea have mechanism by which they can adhere to surfaces and to each other. They will form on virtually every non shedding surface in a non sterile aqueous or very human environment. With reference to the immediate human environment, they can be found growing in shower easily because it provides a moist and warm environment for them to thrive. They also form inside water sewage pipes causing clogging and contributing to about 20% of their corrosion.

Biofilms can also affect marine engineering systems such as pipelines of the offshore oil and gas industry where they may be found causing a substantial corrosion problem. Although corrosion in the circumstance is mainly due to abiotic reasons. Furthermore, bacterial adhesion is the foundation for bio fouling of sea bound vessels. Once a film of bacteria forms, it is easy for other marine organisms such as barnacles to attach. Such fouling can reduce the maximum speed of the vessels by up to 20% therefore prolonging the voyages with resultant extra consumption of fuel.They have also been found to be involved in a wide variety of microbial infections in the body. By one estimate 80% of all infections including intestinal tract infections, dental plaques gingivitis, catheter infections, and middle ear infections have been associated with them (NIH 2002). Most recently, it has been observed that bacterial biofilms may impair cutaneous would healing and reduce topical anti bacterial efficiency in healing or treating

infected skin wounds (Davis et al 2008). In many animals including man, they build up in teeth forming dental plaques and causing gum diseases (Rogers 2008, Mihai et al 2010)

The microbial cells growing in a biofilm are physiologically distinct from planktonic cells of the same organisms which by contrast are single cells that may float or swim in a liquid medium. Microbes form a biofim in response to many factors which may include cellular recognition of specific or non specific attachment sites on a surface, nutritional cues, or in some cases by exposure of planktonic cells to sub-inhibitory concentration of antibiotics (Hoffman et al 2005; Karatan and Watnick 2009). It is suffice to note that biofilms exhibit both negative and positive properties. For instance, many sewage treatment plants include a treatment stage in which waste water passes over biofilms growing on filters which extract and digest organic compounds. In such biofilms, bacteria are mainly responsible for the organic matter, i.e biochemical oxygen demand. (BOD) While protozoa and rotifiers are mainly responsible for the removal of suspended solids including pathogens and micro organisms. Slow sand filters rely on biofilm development in the same way to filter surface water from lake, spring or river sources for drinking purposes. Thus what is regarded as clean water is effectively a waste material to these micro cellular organisms. In addition, biofilms can help eliminate petroleum oil from contaminated oceans or marine systems. The oil eliminated by the hydrocarbon degrading activities of microbial communities, in particular by a remarkable recently discovered group of specialists called "Hydro-carbon-clastic bacteria" (HCB) (Martins dos Santos et al 2008).

Stromatolites are layered accretionary structures formed in shallow water by the trapping, binding and cementation of sedimentary grains by microbial films especially of *Cyanobacteria.* Stromatolites include some of the most ancient aggregated structures on earth and are still forming today. Further, biofilms are also useful in microbial fuel cells (MFC) to generate electricity from a variety of starting materials including complex organic waste and renewable biomass (Lear and Lewis 2012). The social structure i.e cooperation and competition within a biofilm highly depends on the species present (Nadel et al 2009). Bacteria living in a biofilm usually have significantly different properties of free floating bacteria of the same species as the dense and protected environment of the film allows them to cooperate and interact in various ways.One benefit of this environment is increased resistance to detergent and antibiotic as the dense extra cellular matrix and the Outer layer cells protect the interior of the community. In some cases, antibiotics resistance can be increased a thousand fold (Stewart and Costerlon 2001). Furthermore, lateral gene transfer is greatly facilitated in biofilms and this leads to a more stable biofilms structure (Motin and Tolker- Nielen 2003) Other example of acquisition of resistance by organisms in biofilm could be found in the Legionellea bacteria and *Staphylococcus aereus*. *Legionella* bacteria are known to grow under certain conditions in biofilms in which they are protected against disinfectants. Workers in cooling towers, people working in air conditioned rooms and those taking showers are exposed to legionella by inhalation when the systems are not well designed, constructed or maintained (Murga et al 2001). Sub-therapeutic levels of B-lactam antibiotics induce biofilms formation in *Staphylococcus aereus*. This sub-therapeutic level of antibiotics may result from the use of antibiotics as growth promoters in agriculture, improper disposal of unused drugs or products of excretion

during the normal course of antibiotic therapy. The biofilms formation induced by low level methicilin was inhibited by DNAse suggesting that the sub-therapeutic levels of the antibiotic also induce extracellular DNA release (Kaplan et al 2012)

However, biofilms are not always less susceptible to antibiotics. For instance, the biofilms form of *Pseudomonas aeruginosa* has no greater resistance to antimicrobials than do stationary phase planktonic cells, although when the biofilm is compared to logarithmic phase planktonic cells, the biofilm does have greater resistance to antimicrobials. This resistance to antibiotics in both stationary phase cells and biofilms may be due to the presence of persister cells (Spoering and Lewis 2001).

3.1.3. Diethylstilbestrol (DES)

Diethylstilbesterol (DES) is a synthetic estrogen that is used to prevent miscarriages in women between 1940s and 1960s. A moderate increase in breast cancer risk has been shown both in daughter of women who were treated with DES during pregnancy as well as in their granddaughters. The expression of 82 mi RNAs (91% of the 898 mRNAs) evaluated were observed in breast epithelial cell exposed to DES. In particular, the suppression of MIR-9-3 expression was accompanied by promoter hypermethylation of the MIR-9-5 coding gene in DES treated epithelial cells.

3.1.4. Contamination with herbal products: Aristolochic acid

Aristolochic Acid (AA) is a natural compound found in many plants of the Aristolochia genius. 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 (Vancher Weghem et al 1993, Kwak et al 2012,). In the 1990s, epidemiological studies revealed AA exposure was associated with a high risk of nephrotoxicity and upper urinary tract urothelial cell carcinoma (UTUC) (De Broe et al 1999, Grollman et al 2007, Debelle et al 2008, Notier et al 2000) caused by the ability of AA to bind DNA, forming DNA adduct. (Schmeiser et al 1998). These findings, consequently led to ban on the use of 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).In Taiwan, AA associated DNA adducts was detected in the renal cortex of more than 50% of UTUC patients (Moriya et al 2011) and incidence of UTUC of 30% is strikingly higher than in the West with 3% (Yang et al 2002). This figure is consistent with AA playing a role in Asian UTUC. There is a possibility that AA may contaminate surface water, grain and vegetables during the processing of Aristolochia containing herbs and the disposal of its waste. Aristolochia species are commonly used in Chinese herbal medicine (Barceleux 2008 et al, Henrich 2009, Gluhovschi et al 2011). Aristolochic acid I is the most abundant of the Aristolochic acids found in almost all Aristolochia species and are often accompanied by aristolactam which has been implicated as the causative agent of Balkan endemic nephropathy (BEN), Chinese herb nephropathy (CHN) and urethelial cancer (UC). When hay meant for feeding horses was

contaminated with Aristolochia plants, the horses were observed to develop chronic renal failure. (Grollman 2013).

TP 53 mutation signature in urothelial tumours and the presence of aristolaclam DNA adducts in the renal cortex defined in the course of research proved to be a robust bio marker of exposure to this potent nephrotoxin and human carcinogen (Moriya et al 2011). 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. Another common herb which may contaminate the ecosystem is marijuana with the potential ability to interfere with the biological system of aquatic flora and fauna. In addition, herbs like St. John's wort has been observed to cause modulation of Cytochrome p_{450} and may interfere with prescribed therapeutic agents (Guegenrich 1997).

3.2. Toxin-environment interaction

It is a well known fact that toxins interact frequently with the environment and some of these interactions may have deleterious effects on plants animals and man. Some of these effects are discussed further in this chapter.

3.2.1. Autoimmune diseases

There is a current view that environmental exposure play a role in the development and or the exacerbation of autoimmune diseases. (Ritz 2010,Bashir et al 2011). Auto immune diseases result from an immune response directed against the body's own tissues. There are so many different auto immune diseases and though many of the individual immune diseases are rare, autoimmune diseases collectively afflict approximately 24.5million Americans with women disproportionally affected. The causes of auto immune disorders remain largely unknown. During reproductive ages (18-40), there is a distinct female preponderance of autoimmune diseases including and sex hormones and/or sex chromosomes may be responsible for this enhanced susceptibility (Whitcare et al 1999, Voskuhi 2011). Genetic risk factors have been and continue to be studied and account for a portion of the risk for autoimmune disorders with concordance studies in identical; twins generally in the 25 - 40% range. It is becoming clear from human studies as well as animal model and in vitro research that the etiology of autoimmune diseases is multi-factoral involving both genetic and environmental influences.

Existing data and epidemiological evidence supports a role for the contribution of a number of environmental exposures to the development of specific auto immune outcomes. Included in this current line of thought were crystalline silica exposure and the development of several autoimmune diseases including 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, smoking and the development of seropositive RA; and an inverse relationship between ultraviolet radiation exposure and the risk of development of multiple sclerosis (MS).Furthermore, animal models of exposure provide additional support for the role of xenobiotics in the development of autoimmune diseases. Examples of demonstrated links include: forms of inorganic mercury and the induction of a

transient systematic autoimmune diseases in rats and mice and the mineral oil component 2, 6, 10, 14 tetramethylphenylenediamine (TMPD or pristane) and an induction of chronic lupus like disease and inflammatory arthritis in several strains of mice. Animal model studies have shown additional exposures with likely link to the induction and or exacerbation of auto immune diseases, including gold, silica, trichloroethylene (TCE), 2, 3, 7, 8, - Tetra dichloro-dibenzo-p-dioxin (TCDD), organochlorine pesticides and ultraviolet (UV) radiation.The mechanisms by which environmental factors alter basic biological processes to induce auto immune diseases continue to be examined, but remain largely unknown. A growing body of literature points to a number of mechanisms likely involved in environmental exposure-based auto immunity and include a role for xenobiotics in the activation of Toll-like receptors (TLR); 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. The cumulative body of research findings is increasing the confidence that specific exposures and mechanisms are involved in the development of auto immune diseases. Despite growing advances in the field, an understanding of the interactive roles of the environment and genetics in the auto immune process is still lacking and additional progress is needed on many fronts (NIEHS).

3.2.2. Endocrine disruptors

An important aspect of environment toxin interaction (TXE) is the effects of endocrine disruptors on aquatic system (Le Parge et al 2011). Environmental xenobiotics having oestrogenic effects include plants, pesticides, surfactants, plastics and animal genistein, methoxyclor and bisphenol. They cause lowering of cholesterol on oestrogen dependent animal models and have been associated as a cause of osteoporosis. Endocrine disruptors (EDC) are chemicals that may interfere with the production or activity of hormones in living organisms. Perhaps are the synthetic hormonal drugs such as birth control pills. Others are dioxins polychlorinated biophenyls (PCB) pesticides, bisphenol A, phthalates, lead, mercury cadmium, arsenic herbicides; atrazine, plastic residues, and cleaning products. These chemicals can enter the aquatic system through improper medical waste disposal, runoff from land fill and sewage discharge from storms (Daughton and Ruhoy 2008, Fent 2006, Genius et al 2012).

3.2.2.1. Wildlife

Because a large proportion of potential endocrine disruptors end up in surface waters, aquatic species are particularly vulnerable to their potential adverse effects. Recent studies identified a number of brain targets for EDC commonly present in environmentally relevant concentrations in surface waters. Among those normal systems disrupted by EDC are the gonadotrophin releasing hormone (GnRH) neurons, the dopaminergic circuits and more recently the Kiss/GPR54 system, which regulates gonadotrophin release. However, one of the most striking effects of EDC, notably estrogen mimics, is their impact on the Cyp19a1b. gene that encodes the brain aromatase isoform in fish. This is an example in which the molecular basis of endocrine disruption is fully understood. (Le Page et al 2011). More commonly observed effects of EDC is impaired reproduction and development in aquatic

animals (Kidd el al 2007). Furthermore, masculinization (imposex) had been observed in female marine snails exposed to tributylin (TBT), a biocide used in anti-fouling paints. The dog whelk "(*Nucella lapillus*) a species of predatory sea snail' after is particularly sensitive and imposex has resulted in decline or extinction of local populations worldwide, including coastal areas all over Europe and in the open North Sea. DDE – induced egg-shell thinning in birds is probably the best example of reproductive impairment causing several population declines in a number of raptor in species Europe and North America. Developmental exposure to the DDT complex has been formerly linked to the induction of ovotestis in male western gulls. EDGs have adversely affected a variety of fish species in the vicinity of certain sources, for example effluents of water treatment and in the most contaminated areas, this exposure is causally linked with effects on reproductive organs which could have implication for fish populations. Turtles can also be affected in the in the same way (Cleuvers 2003,Le Parge et al 2011).

In mammals, the best evidence came from the field studies on Baltic grey and ringed seals and from the semi-field studies on Wadden Sea harbour seals, where both reproduction and immune function hare been impaired by PCBs in the food chain other mammals affected include the polar bear, rabbit and guinea pig. Distorted sex-organ development and function in alligators has been linked with a major pesticide spell into a lake in Florida in USA. Furthermore, the oestrogenic and androgenic effects observed in this reptile have been causally linked in experimental studies with alligator eggs to the DDT complex. For terrestrial (land living) wildlife, including aquatic mammals, exposure is primarily expected to be of dietary origin. The situation is however different for aquatics wild life where direct uptake of dissolved chemicals from the water is a significant route to exposure.

3.2.2.2. Effect on humans

The possible pathway of exposure to endocrine disruptors in humans, include, direct exposure at work place, 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.

In general, the vulnerability of a given species will depend on the intrinsic properties of the chemical, magnitude, duration, frequency means of exposure and the way in which a given specie can absorb, distribute, transform and eliminate substances. It will also depend on the sensitivity of specific organ at different stages of development.The endocrine- disruptor hypothesis was originally formulated for xenoestrogens i.e chemical which affect the estrogen signaling pathway. The greatest attention to endocrine disruption has focused on estrogenic effects but a clear cause-effect relationship has not yet been established. (Meeker 2012, EC2013,)

However, it is now becoming generally accepted that compounds of various types can interact with different component in several cell regulatory systems including the steroid and thyroid hormone receptor families. Apart from the drug DES (synthetic oestrogens), environmental oestrogens have never been proven to cause human health problems. At best there can only be speculation on possible human health effects by interpolation of documents obtained from animal studies (Hollander 1997) EDCs which act via receptors of the steroid receptor super family can have effect on many organs of the body. Steroid receptors for oestrogens, androgens

http://dx.doi.org/10.5772/57473

and adrenocorticoid and thyroid hormones are found in practically all cells of the body. The functions of the brain, the cardiovascular, the skeletal and the urogenital system are regulated by these hormones and can therefore be affected by EDCS. In addition, an EDC with a defined action in one organ; for example estrogenic activity can extent similar or non-oestrogenic effect or even antagonistic effects in other organs.

3.2.2.3. Potential effect in males

EDCS has the potential to cause poor semen quality including low sperm counts, low ejaculate volume, high number of abnormal spermatozoa motility. Other effects may include testicular cancer, malformed reproductive tissue. viz undescended testes, small penis size, prostate disease and other unrecognized abnormalities of male reproductive tissues. In infertility studies, the effects of environmental pollution including occupational exposures are currently being given due consideration.

3.2.2.4. Potential effect in females

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.

3.2.2.5. Potential effect in children

EDCS have been linked with impaired behavior, mental, immune and thyroid functions in developing children. Other include precocious puberty, osteoporosis, foetal growth, child development, and obesity (Meeker 2012)

3.3. Environmental pharmacology and the pediatrics population

Although non therapeutic xenobiotics represent the vast majority of environmental exposures during childhood, studies of these compounds in children has lagged behind drug studies.The paediatric group is unique with respect to environmental contaminants in that there is a lot of hand to mouth activities ranging from food stuff to drug and plastic toys. They are also quite vulnerable to poisoning from unprescribed medications. However, an increased impetus for paediatric pharmacology studies resulted from evidence of short comings in algorithmic approaches to dosing and the recognition of differing efficacy. While in some drugs developmental differences resulted in increase toxicity or failed efficacy. In others decreased toxicity was observed and toxicity in children compared to adults. Thus the paediatric patients may not be classified arbitrarily as a susceptible population, but however, certainly a different group compared with the adults. Better designed pediatric pharmacology studies use well documented, non linear changes in body composition across childhood, as well as knowledge about the impact of physical growth, mediated by complex normal changes. Developmental differences in all component of drug disposition, including absorption, distribution, metabolism and excretion have been characterized. Of these, the ontogeny of metabolism, particularly tissue specific metabolism, is the most complex. Many knowledge gaps still persist within

developmental pharmacology (McCarver 2004). The most common concern for pediatric environmental pharmacology are the EDCs. While human epidemiology studies of exposure to EDCs and children's health remain extremely limited, a growing body of evidence show that exposure to a number of chemicals commonly found in consumer goods, personal care products, food drinking water, and other sources may adversely affect child development through altered endocrine function. Some of which include persistent organic pollutants (POP) phthalates, bisphenol A and contemporary use pesticides had earlier been discussed in this chapter.

Each year, nearly 1,500 children under 6 years old are treated in U.S. emergency department as a result of accidental ingestion of buprenorphine. A new study examines 2,3800 of these cases for October 2009 to March 2012. Buprenorphine brand name (subutex) is used alone or in combination with another drug called naloxone (brand name suboxone) to ease the symptoms of withdrawal in people trying to beat addictions to herein, certain prescription pain killers and other opoid drugs. One dose of this medication can be fatal to a small child. Other commonly used medications such as high blood pressure medicals, some diabetic drugs, strong pain killers, some medications used for arthritis, and some drugs for attention deficit/hyperactivity disorder can potentially be fatal to a small child with just a single dose. (Lavonas 2013).

3.4. Miscellaneous toxicity

Bisphenol A, a component used in many plastic products binds to the local anaesthetic receptor site to block the human cardiac sodium channel (O Really et al 2012). Nickel, chromium arsenic and lead are well known environmental toxicant. Many household products like insecticides, paints, cosmetics, cleaning fluids, nano-materials based items are known to contain some of these toxicants. While they may not be directly toxic, their interaction with cellular organelles may result in cancer. Lead is known to be hepatotoxic while cadmium is a well known nephrotoxic agent. Phthalates which is commonly used in cosmetics like nail polish are thought to affect the endocrine system and are being investigated for a link with infertility in women

3.4.1. Household products

Many household products are potentially dangerous substances, and these include oven and drain cleaners, laundry powder, floor polish, paint and pesticides. Even arts and craft supplies and yard care products can be hazardous. Many household products can harm children pets and the environment if not correctly stored, used and disposed of. Toxic substances in these products can cause harm if inhaled, swallowed or absorbed through the skin.

Based on genetic composition, people respond to toxic substance might cause birth defects or other sources problems including brain damage or death. The concept of 3Rs viz reduction, reuse and recycling is bound to minimize amount of drugs in the environment.

Household waste (HHW): reduction, reuse, recycling and finally disposal

- Reduction and recycling of HHW conserves resources and energy that would be expended in the production of more products

http://dx.doi.org/10.5772/57473

- Re use of hazardous household products can save money and reduce the need for generating hazardous substances
- Proper disposal prevents pollution that could endanger human health and the environment

3.4.2. Pesticides

Pesticides can be fungicides, herbicides and rodenticides. Pests live where they are not wanted or cause harm to crops, people or animals and pesticides have been useful agents in getting rid of them..Pesticides can be very helpful in the sense that they protect man's health by killing germs, animals or plants that can hurt us. However, most pesticides can be harmful to people and pets. Disposing of pesticides properly is also important as it can protect the environment. Biologically based pesticides are becoming more popular as they often safer than traditional pesticides. They come in the form of pheromones and microbial pesticides.

Pesticides are classified as semi volatile organic compounds and include a variety of chemicals in various forms. They are chemicals that are used to kill or control pests which include bacteria, fungi and other organisms. In addition, to insects and rodents Pesticides are inherently toxic. Health effects of pesticides include irritation to eye, nose, throat, damage to central nervous system and kidney and increased risk of cancer. Symptoms of pesticide toxicity include headache, dizziness, muscular weakness and nausea. Chronic exposure to some pesticides can result in damage to the liver, kidneys, endocrine and nervous systems both the active and inert ingredients in pesticides can be organic compounds; therefore, both could add to the levels of airborne organics inside homes. Furthermore, both types of ingredients can cause the type of effects obtained in either house hold chemical products like those seen in volatile organic compounds (VOCs). However, as with other household products, there is an insufficient understanding at present about what pesticide concentrations are necessary to produce these effects. Exposure to high levels of cyclodiene pesticides commonly associated with misapplication had caused various symptoms, including headaches, dizziness, muscle twitching, weakness, tingling sensation, and nausea. It is also thought that cyclodienes might cause long-term damage to the liver and the central nervous system as well as an increased risk of cancer. Subsequently, in the U.S, no further sales or commercial use were permitted for the following cyclodiene or related pesticides: chlordene, aldrin, dieldrin and heptachlor. The only exception however is the use of heptachlor by utility companies to control fire ants in underground cable boxes.

Safe pesticides

Ninety percent of pesticides currently in use are synthetic, however, in the last two decades 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. It has also become increasingly likely that some synthetic pesticides such as (DDT), were not poor choices, but misused and overused thus leading to many reputable environmental groups urging that the use of DDT be reconsidered because its effectiveness is unrivaled and causes minimal collateral damage when properly applied. At the same time, organic pesticides are becoming increasingly effective and affordable. They now command

over 10% of the pesticide market in the United States. The paradox of organic or biopesticides is that the product and genetically engineered organochlorine is natural, being a fungus, virus or bacteria making it an interesting products to the environmentalists. Synthetic pesticides such as organophosphate and organchlorine insecticides have been associated with everything from cancer to neurological disorders and lung irritations in humans. However, these symptoms are unlikely, if not impossible to get from a healthy dose of fruits or vegetables. A variety of pesticides such as mineral oil, malathion, sulphur dimethylamine and many others re used to control fungi and insects on wheat and cereals. It is therefore naïve to think that humans can totally avoid ingestion of pesticides. 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. Healthy humans can detoxify the body over time and the levels are rarely high enough to do any real harm (Ecoworld 2004).

Biological pesticides or biopesticides

Biological pesticides are pesticides based on microorganisms or natural products (Coombs 2013). They are typically created by growing and concentrating naturally occurring organisms and or their metabolites including bacteria and other microbes, fungi, nematodes, proteins etc. They are often considered to be important components of integrated pest management (IPM) programmes and have received much practical attention as substitutes to synthetic chemical plant protection productions (PPPs). (Coping 2009). Biopesticides are divided into three major classes and these include:

i. Microbial pesticides which consist of bacteria, entomopathogenic fungi or viruses and sometimes includes the metabolites that bacteria of fungi produce. Entomopathogenic hematodes are also often classified as microbial pesticides, even though they are multi-cellular (Coombs 2013).

ii. Biochemical pesticides: these are naturally occurring substances that control or monitor in the case of pheromones, pests.

iii. Plant: incorporated protectants (PIPs): which have genetic material from other species incorporated into their genetic material i.e. genetically modified crops (GMCs). There have been a lot of controversies on (GMSs). In many European countries it is pertinent to note that apart from the biological activity of biopesticides against insect pests, nematodes, fungi and other organism, they usually have no known function in photosynthesis, growth and other basic aspects of plant physiology.

Applications of biopesticides is similar to chemical pesticides and are becoming widely used due to their environmental friendliness and biodegradability.

Examples of biopesticides include

i. *Bacillus thuringiensis* toxin, (BE Toxin) genetically incorporated into plants as insecticide. There is however controversies associated with use of BT toxin which has been observed to have a negative impact on the liver and kidneys of mammals with contaminated Bt toxin in their diet (Kilie and Akay 2008).

http://dx.doi.org/10.5772/57473

ii. Entomopathogenic fungi (e.g. *Beauveria bassiana, Lacanicillum spp, Metarinzium spp*.

iii. Disease controling agents such as *Trichoderma spp* and *Ampelomyces quisqualis*

iv. Beneficial nematodes attacking insects e.g. *Sleinernema fetiae* or slug pest such as *Phasmarhabditis hermaphrodita*.

v. Entomopathogenic viruses e.g. *Cydia pomonella granulo virus*.

vi. Insect pheromones and other semio chemicals.

vii. Fermentation products such as spinosad (a macro-cylic lactone)

viii. Chitosan: a plant to which this product is applied will naturally induce systemic resistance to allow the plant to defend itself against disease, pathogen and pests (Benhamou et al 1994).

ix. Natural plant derived products such as alkaloides terpenoids, phenolics and secondary chemicals. Certain vegetable oils are known to have pesticidal properties. In addition, products based on extracts of plants such as garlic have now been registered in the European Union and other places.

x. Naturally occurring minerals such as baking soda are also thought to have pesticide properties.

Biopesticides have advantages and disadvantages over the conventional chemical pesticides and these advantages include non detection of harmful residues, cost effective, biodegradable and in some cases more effective Their disadvantages include high specificity, slow pace of action, variable efficacy and the potential of ability of target organism to acquire tolerance as living organisms evolving.

3.4.3. Triclosan

Triclosan (TCS) is a broad spectrum antimicrobial compound that is incorporated into numerous consumer products. Triclosan which is contained in about half of liquid soaps functions by slowing or stopping the growth of bacteria, fungi and mildew. Triclosan frequently gets into streams and rivers through domestic waste water, leaking sewerage and sewage overflows. The bacterial resistance caused by triclosan was found to disrupt aquatic life by changing natural bacterial communities leading to emergence of resistance bacteria that could diminish the usefulness of important antibiotics (Drury et al 2013).

3.4.4. Criminal Environmental xenobiotic pollution

There had been recent cases of pollution of the environment with criminal intents. One of the most notable is the use of Aldicarb (Temik) a carbamate insecticide which is extremely toxic to mammals and has been widely used by wildlife poachers in South Africa for many years to poison rhinos and other wild life species. Aldicarb is also used by burglars to poison sentry dogs, and the general public to destroy rats and stray dogs. Although banned in South Africa, it is readily available in Zimbabwe and Mozambique and large quantities are smuggled into South Africa for illegal sale there.

Temik is widely used normally as a pesticide on crops such as cotton, potatoes and peanuts and it is registered under the terms of The Fertilizers, Farm Seeds, Agricultural and Stock Remedies Act of 1947. As a member of the carbamate pesticides, classification is divided into super high and medium toxicity. By implication, it falls within the super toxic class which males its highly toxic. It takes ½ - 1½ hour for symptoms to show and intoxication lasts up to six to eight hours. Fatality is due to asphyxiation as the lungs are flooded with secretion from the stomach. A teaspoon is enough to kills a grown rhinoceros while 1 μg can kill a rodent, making it more poisonous than arsenic. Rhinos are targets in Africa and Asia for their horns which fetch high prices in Yemen where they are prized for making dagger handles and in East Asia where they are used in traditional medicine Application of Temik and other xenobiotics like cyanide for criminal intent of poaching is by lacing watering holes of the animals with the said substances. (Promed 2013)

Successful treatment of animals poisoned with aldicarb is the timely treatment with anti-muscarinic drugs such as atropine with additional supportive treatment options including fluid therapy, diphenylhydrazine, benzodiazepams and prevention of further absorption using activated charcoal (Amot et al 2011). Early treatment can be very successful. In areas like South Africa where such practice is endemic, pet owners are advised to keep their dogs inside or in a backyard at night and pets should be fed at night to prevent them from eating poisoned baits. Furthermore obedience training of dog to prevent food acceptance from strangers is also advised. At one of the veterinary clinics in Gauteng Province in South Africa, in 2003, 97 cases of aldicarb poisoning were diagnosed (Amot et al 2011). However, the intentional, malicious poisoning of dogs and other species is not restricted to South Africa alone, there are reports of other large scale practices in USA and Spain (Wassem et al 2012). It has also been reported that aldicarb is illegally used as a household rodenticide in Brazil and the Carribean Island and sometimes human beings are victims. (Ragoucy-Sengler 2000).

3.4.5. Natural health products (NHPs)

Recent evidence have shown that natural health products (NHPs) therapies are increasingly recommended by various health providers, including conventional physicians leading to increased consumption of vitamins and many herbal agents worldwide. According to WHO estimates, the present demand for medicinal plants is about US $14 billion a year and it is estimated to likely increase to about $5 trillion by the year 2050. The high prices and sometimes established side effects of synthetic drugs have caused many people to find alternatives in herbal medicine when faced with options. There are however concerns about safety and efficacy of herbal medicine due to lack of regulation and some reported adverse effects. Although the WHO has developed guidelines for the quality control of herbal drugs which provide a detailed description of the techniques and measures required for the appropriate cultivation and collection of medicinal plants, there is still a lacuna between this available knowledge and implementation because the cultivators of herbs for medicinal uses are usually unaware of the regulations and these products may be contaminated with banned pesticides, microbial agents like fungi, heavy metals and chemical toxins which may cause adverse outcomes such as sensori-neural defects, congenital paralysis, liver and kidney damage. These

http://dx.doi.org/10.5772/57473

contaminants may be related to the source of the herbal drugs. Chemical toxins may come from unfavorable post harvest techniques, wrong storage conditions or through chemical treatment during storage period. Some of these environmental factors may be controlled by implementing good source; good agricultural practices and standard operating procedures (SOP) for producing good quality herbal products.

In a recent study conducted in Boston, USA on Indian ayurvedic medicines, it was observed that ayurvedic medicine obtained from 30 South Asian store in the Boston area had potentially harmful levels of lead, mercury and arsenic. These metals were found in the products like "bal guti", mahayograj guggulu", mahalaxmi vilas ras" safi, shilajit and etc in some of the leading stores within the ayurvedic communities. Therefore, users of the medicines may be at risk of heavy metal toxicity similarly; Koh and Woo (2000) reported excessive toxic heavy metals in Chinese proprietary medicine in Singapore during the year 1990-1997.

In addition Wong et al (1993) also reported concentration of nine heavy metals; viz cadmium, cobalt, copper, iron, manganese, nickel lead, zinc and mercury in 42 Chinese herbal drugs. The concentration range of the stores of metals were comparable to that reported in many of the East Asian vegetables and fruits. Few samples contained a higher concentration of toxic metals such as calcium, lead and mercury. This report suggested that the presence of heavy metals was probably caused by contamination during air drying and preservation (Rai and Mehrotra 2005). Whether an element is toxic or not is determined by many factors including route of exposure, dose, site of accumulation, nutritional status, detoxification biochemistry and the particular form of species in which the elements exists within the body. Different species of elements have the potential to display distinct toxicity patterns for example, hexavalent chromium (chromium VI) is highly toxic and carcinogenic while trivalent chromium (chromium III) is an essential metal involved in lipid and carbohydrate metabolism.Similarly, inorganic and organic arsenic are both naturally occurring compounds that display different toxicities. While certain inorganic arsenic species are classified as human carcinogens, some form of organic arsenic such as arsenobetaine (which accumulates in some aquatics organisms such as shrimp) are relatively non – toxic specific forms of some elements also have the potential to be converted within the body to different forms; which changes their properties and potential toxicity.

Most natural health products tested showed detectable contamination with one or more toxic elements, the degree of contamination appears to be linked to the country of manufacture with higher contamination from mercury, arsenic and aluminum primarily found in products imported from China. Marine –sourced NHPs usually have the highest level of lead contamination while non-marine sourced NHPs manufactured in North America generally demonstrated the least contamination among samples tested. Although marine sourced and ayurvedic NHPs were almost often contaminated, the levels rarely exceeded established toxicity guidelines (Genius et al 2012).

3.4.6. Chlorination of water

The most common disinfection method involves some form of chlorine or its compounds such as chloramines or chlorine dioxides. Chlorine is a strong oxidant that rapidly kills many

harmful micro organisms. Because chlorine is a toxic gas, there is a danger of a release associated with its use. This problem can be avoided by the use of sodium hypochlorite, which is a relatively inexpensive solution that releases free chlorine when dissolved in water. The generation of liquid sodium hypochlorite is both inexpensive and safer than the use of gas or solid chlorine. One drain back is that chlorine from any source reacts with natural organic compounds in the 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 United States of America by the Environmental Protection Agency. For example, rats chronically intoxicated with triethylin drinking water, demonstrated cerebral oedema as well as an increase in phosphatidyl ethanolamine-n-methyl transferase activity. The increased methylation might be a compensatory mechanisms for counteracting the membranes damages induced by triethylin. Furthermore, chloroform, dichloroacetic acid (DCA) and trichloroacetic acid (TCA) which are known liver and kidney carcinogens are by product of chlorine disinfection found in drinking water. In mice treated with these three chlorine by products, hypermethylation and increased expression of c-myc-c a proto-oncogene involved in liver and kidney tumours were observed. Trihalomethanes viz chloroform, bromo-dichloromethane, chloro-bromomethane and bromoform are regulated organic contaminants in drinking water. Experimental evidences in the female B6C3F1 mouse liver demonstrated carcinogenic activities of the tri-halomethanes. Chloroform and bromo-dichloromethane were observed to decrease the concentration of 5- methyl-cystosine in hepatic DNA. Methylation in the promoter region of the c-myc gene was reduced by the tri-halomethanes, a process consistent with carcinogenic activities. The formation of THMs and haloacetic acids may be minimized by effective removal of as many organics from the water as possible prior to chlorine addition. Although chlorine is effective in killing bacteria, it has limited effectiveness against protozoa that form cysts in water (*Girdia lamblia* and *Cryptosporidium*, both of which are pathogenic).

Alternatives to elemental chlorine disinfection include chlorine dioxide disinfection, chloramines disinfection, ozone disinfection and ultraviolet disinfection.

i. Chloride dioxide disinfection: Chlorine dioxide is a faster acting disinfection than elemental chlorine. It is relatively rarely used because in some circumstances it may create excessive amount of chlorite, which is a by-product regulated to low allowable levels in the United States. Chlorine dioxide is supplied as an aqueun solution and added to water to avoid gas handling problems, chlorine dioxide gas accumulations may spontaneously detonate.

ii. Chloramines disinfection: the use of chloramines is becoming more common as a disinfectant. Although chloramines is not as strong as oxidant, it does provide a longer-lasting residual than free chlorine and it won't form THM's or haloacetic acids. It is also possible to convent chlorine to chlorine by colding ammonia to the water after addition of chlorine. The chlorine and ammonia reacts to form chloramines.

3.5. Gene environment interaction (GXE)

Every human start life with a particular set of genes of about 20,000 to 25,000. Chemicals may not necessarily cause mutation of genes but may send subtle signals that silence them or switch them on at the wrong times. Chemicals in our environment and food can alter the genes, leaving the exposed, vulnerable to a variety of diseases and disorders including diabetes, asthma, cancer, and obesity. It may therefore be expedient to start testing chemicals for these effects.

3.5.1. Toxicogenomics: environmental epigenetics

Toxicogenomics is a field that emerged from conventional toxicology with functional genomics. In recent years, this field contributed immensely in defining adverse biological effects resulting from environmental stressors; toxins, drugs and chemicals. Through micro array technology, large scale detection and quantification of mRNA transcripts and microRNA related to alterations in mRNA stability or gene regulation becomes feasible. Other omics technologies, notably proteomics and metabolomics soon joined in providing further fine turning in the gathering and interpretation of toxicological data. A field that will inevitably modify the landscape of toxicogenomics is epigenetics, a term referring to heritable changes in gene expression without the accompanying alterations in the DNA sequence. These epigenetic changes may result from mechanism such as DNA methylation, histone modification and non coding RNAs in the regulation of gene expression. Epigenetic mechanisms are essential in normal development and differentiation but these can be misdirected leading to diseases notably cancer. There is now a mounting body of evidence that environmental exposure particularly in early development can induce epigenetic changes which may be transmitted in subsequent generations or serve as basis for diseases developed in later life. Either way, epigenetic mechanisms will help interpret toxicological data or toxicogenomic approaches to identify epigenetic effects of environmental exposures. Thus a full understanding of environmental interactions with the genome requires keeping abreast of epigenetic mechanisms as well as conducting routine analyses of epigenetic modifications as part of the mechanisms of actions of environmental exposure. For example epigenetic modification was observed in the tumour suppressor gene Tsrc1 (1-gsf4a) obtained from transgenic mouse models.

The genome is dynamic and responsive to environmental signals not only during development but also throughout life and it is becoming increasingly apparent that chemicals cause the changes in gene expression that persist long after the exposure has ceased. Commonly used pharmaceutical drugs can cause persistent epigenetic changes. By altering epigenetic homeostasis by direct or indirect mechanisms. Direct effects may be caused by drugs which affect chromatin architecture or DNA methylation. For example the anti-hypertensive hydrazine inhibits DNA methylation while isotretinoin has transcription factor activity. A two tier mechanism is postulated for indirect effect in which acute exposure to a drug influences signaling pathways that may lead to an alternative of transcription factor activity of gene promoters. This stimulation results in the altered expression of receptors signaling molecules and other proteins necessary to alter genetic regulatory circuits. With more chronic exposure,

cells adapt by an unknown process that results in more permanent modification to DNA methylation and chromatin structure leading to enduring alteration of a given genetic network. Therefore, any genetic side-effects caused by a drug may persist after the drug is discontinued.

Some iatrogenic diseases such as 'tardive dyskinesia' and drug induced systemic lupus erythematosis (SLE) may be epigenetic in nature. Furthermore, epigenetic side effects of pharmaceuticals may be involved in the aetiology of heart disease, cancer neurological and cognitive disorders, obesity, diabetes, infertility and sexual dysfunction. It is suggested that a systems biology approach employing micro array analyses of gene expression and methylation patterns can lead to a better understanding of long term side effects of drugs and in future epigenetic assays should be incorporated into the safely assessment of all pharmaceuticals drugs. Some environmental chemicals enable methyl group to attack normal genes turning them off or muting them at a time when they should be turned on. When such genes are turned off, they can't direct the manufacture of proteins that are essential for proper cell function. Chemicals can also uncoil parts of the chromosomes causing genes to be expressed or turned on at inappropriate times. In a recent study in New York City, it was observed that children exposed in the womb to high levels of polycyclic aromatic hydrocarbons (PAH), a common air pollutant from traffic emissions were more likely to have asthma than those not exposed. Using cord blood for the analysis, it was observed that a particular gene (AC SL3) was methylated in the exposed children but not methylated in the unexposed ones. The result was suggestive that the abnormal methylation pattern probably caused the asthma. (Weksberg et al 2010).

Epigenetic changes have also been observed with children conceived with assisted reproductive technologies. One of the disorders that occur at a higher rate in these children is 'Beckwith-Wiedemann syndrome', a disease characterized by abnormal wall defects and a higher risk of certain childhood cancer (Weksberg et al 2010). Beckwith-Wiedemann syndrome is a condition that affects many parts of the body. It is classified as an overgrowth syndrome, which means that affected infants are considerably larger than normal (macrosomia) and continue to grow and gain weight at an unusual rate during childhood. Growth begins to slow by about age 8, and adults with this condition are not unusually tall. In some children with Beckwith-Wiedemann syndrome, specific parts of the body may grow abnormally large, leading to an asymmetric or uneven appearance. This unusual growth pattern is known as hemihyperplasia The signs and symptoms of Beckwith-Wiedemann syndrome vary among affected individuals. Many people with this condition are born with an opening in the wall of the abdomen (an omphalocele) that allows the abdominal organs to protrude through the navel. Other abdominal wall defects, such as a soft out-pouching around the belly-button (an umbilical hernia), are also common. Most infants with Beckwith-Wiedemann syndrome have an abnormally large tongue (macroglossia), which may interfere with breathing, swallowing, and speaking. Other major features of this condition include abnormally large abdominal organs (visceromegaly), creases or pits in the skin near the ears, low blood sugar (hypoglycemia) in infancy, and kidney abnormalities. Children with Beckwith-Wiedemann syndrome are at an increased risk of developing several types of cancerous and noncancerous tumors, particularly a rare form of kidney cancer called Wilm's tumor, a cancer of muscle tissue called rhabdomyosarcoma, and

a form of liver cancer called hepatoblastoma. Tumors develop in about 10 percent of people with this condition and almost always appear in childhood. About one in five infants with Beckwith-Wiedemann syndrome dies early in life from complications related to the disorder. Older children and adults are much less likely to have serious medical problems associated with the condition. With respect to in vitro fertilization, it was postulated that the culture medium where fertilized eggs were grown for several days before implantation probably caused the syndrome. The possibility that the different media used for the eggs might contain a chemical contaminant that stimulate the addition of methyl group to the cells.

Some toxic metals have also been implicated to having epigenetic effects. For example nickel, chromium and arsenic are well known not because they are toxic to cells, directly but due to the fact that they cause increased DNA methylation which may result in gene silencing, cell transformation and subsequently cancer (EHN 2011)

3.5.2. Histone modifications

In humans, protection and packaging of the genetic materials are largely performed by histone proteins which also offer a mechanism for regulation of DNA, transcription, replication and repair. Histone are nuclear globular proteins that can be covalently modified by acetylation (AC) methylation, phosphorylation, glycosylation, sumoylation ubiquitination and adenosine diphosphale (ADP) ribosylation thus influencing chromatin structure and gene expression. The most common histone modification that have been observed in environmental chemical exposure are acetylation and methylation of lysine residues in the amino terminal of histone 3 (H3) and H4. Histone acetylation with only a single acetyl group added to each amino acid residue usually increases gene transcription activity. Whereas, histone methylation found as mono (me) dimethyl (me2) and trimethyl (me3) groups states can inhibit the increased gene expression depending on the amno acid position that is modified.

3.5.3. Environmental antibiotic resistome

Antimicrobial drug resistance is caused by microbial gene products that attenuate the activity of an antibiotic in an otherwise- drug sensitive organism. Bacteria easily acquire resistance gene even in the absence of selection. Hospitals are well known hot spots for the acquisition amplification and dissemination of resistance genes because of the steady supply of strong selective pressure through the prevalent use of antibiotic therapy (Gaze et al 2013)

The failure of antibiotics that were previously effective in controlling infectious diseases is a serious phenomenon that gravely affects the human health. The gene that confers resistance to pathogen was thought to originate from non pathogenic environmental microbes. This environmental resistome, its mobilization and the conditions that facilitate its entry into human pathogens are at the heart of the current public health crisis in antibiotic resistance. Therefore understanding the origins, evolution and mechanism of transfer of resistance elements is vital to the ability to adequately address this public health issue. Recent advances in microbial ecology have revealed the extensive presence of antibiotic resistance genes in environmental bacteria from human polluted; agricultural and pristine soils. The bioactive

products and the mechanism for resistance are diverse bearing in mind the varieties of microbes on the earth. The environmental resistome offers a vast reservoir of genes that have the potential to be mobilized into the antibiotic drug-sensitive cadre of bacterial human pathogens.

One of the distinctive characteristics of microbial genomics is the movement of genes vertically through populations by cell division and horizontally across species and genera. This movement is enabled by the "mobilome", the genetic element that enable and contribute to the horizontal gene transfer (HGT) (Si et al 2009). The mobilome is key to the spread of genes encoding resistance to antimicrobial drugs and heavy metals and for pathogenic traits among bacteria. Because these functions are often co-located on the same mobile elements, selection for 1 phenotype inadvertently selects for its unintended (and often recognized) companion. For example, selection for heavy metal or biocide resistance is often accompanied by antimicrobial drug resistance elements selection for resistance to 1 drug can co-select for 1 of many other (45 genes in 1 notable example) The scale of genetic transfer ranges from short gene segments to mega-bases of DNA depending on the transfer mechanism involved. Thus, even physically distant genes can be co-selected. These facts form a reality that offers cautionary tales for the substitution of 1 drug for another in response to resistance in clinical or agricultural setting or for the use of metals (or exposure to them) that can co-select for antimicrobial drug resistance. Furthermore, plasmids can encode toxin/antitoxin systems that result in plasmid addiction even in the absence of selection. The net result is an exploded mobile meta-genome of shared genetic traits that is fluid and readily promulgated through microbial populations. The rapid movement of water, plants, animals, soil, and humans across the planet virtually ensures that such traits and associated organism, once easily ecological segregated, can move seamlessly through habitats across the globe. The result is that no regions are safe or can escape the introduction and movement of antimicrobial drug-resistant organisms and their genes.

In addition, the antimicrobial drugs themselves, toxins and other compounds can favour genetic exchange and increase genetic diversity. Three principal mechanisms are involved in HGT and these include; conjugation (direct cell to cell transfer), transduction (phage-assisted transfer) and natural transformation (DNA to cell transfer). These mechanisms mobilize genetic elements such as plasmids, genetic islands and phages that can contain resistance elements (Colomer-Llurch et al 2011). The environmental hot spots for horizontal gene transfer (HGT) have been identified and they include the soil particle pores, air-water interfaces in the aquatic environments and biofilms formed on multiple surfaces. Other hot spots include sewage treatment plants where a wide range of chemicals meet human and environmental bacteria in high numbers and manure lagoons where bacterial densities and antimicrobial drug concentrations can be very high and exposure periods lengthy; aquaculture ponds that are routinely treated with antimicrobial drugs, biofilters used in degrading pesticides and environments contaminated by discharge from waste water treatment plants from antimicrobial drug manufacturing. It is therefore instructive that all efforts should be made to minimize the release of antibiotics into the environment.

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3.5.4. Insecticide resistance gene in insects: the case of bed bugs (Cumox lecturlaries)

Perhaps one of the fall out of environmental pollution with insecticides is the development of resistance gene in insects. Although no putative link has been proven, recent discovery of resistance genes in bed bugs makes it plausible. Recent advances in genomic and post genomic technologies have facilitated a genome wide analysis of the insecticides resistance - associated genes in insects. A good example is the observation of resistant genes in bed bugs. Bed bugs (*Cumox lecturlaries*) are parasites that suck human blood. They come out at night and take five to eight minutes to feed and then return to cracks and crevices where they aggregate. In a recent study, a survey of the entire genome of 21 different bed bug population from cities around the Midwestern region of the United States of America (USA), identified 14 genes (molecular markers) that are associated with pyrethroid resistance. Pyrethroids are the chemicals that have been used as the first-line agent against bed bug infestation. Most of the resistance associated genes are functioning in diverse mechanisms and are expressed in the epidermal layer of the integument, which could prevent or slow down the toxin from reaching the target sites on the nerve cells where an additional layer of resistance (kdr) is possible. This strategy that has evolved in bed bugs is based on their unique morphological, physiological and behavioural characteristics and has not been reported in any other insect species. RNA interference – aided knock down of resistance associated genes showed the relative contribution of each mechanism towards overall development. Blocking these special genetic defenses in the laboratory is a relatively straight forward process. The bugs were simply injected with strands of RNA that interfere with gene expression. When these genes are blocked, the bed bugs once again became susceptible to pyrethroids. The challenge now is how to transmit strands of interfering RNA to wild bed bugs. Furthermore, understanding the complexity of adaptive strategies employed by bed bugs will help in designing the most effective and sustainable bed bug control methods (Zhu et al 2013)

4. Pharmaceutical disposal and environment standard

4.1. Good manufacturing practice (GMP)

Good manufacturing practice or (GMP) are practices and the systems required to be adapted in pharmaceutical manufacturing, quality control, quality system covering the manufacture and testing of pharmaceutical or drugs including active pharmaceutical ingredients, diagnostics, foods, pharmaceutical industry in over one hundred countries worldwide, primarily in the developing world. So far, emissions into the environment are not included.

4.2. Disposal of unused medicines

Although medicine play an important role in the treatment of many conditions and diseases, when they are no longer needed, it is important to dispose of them properly to avoid harm to others and the environment. Some of the well established methods of disposal include.

i. Medicine take back programs: this is are good way of removing expired, unwanted or unused medicine. In most advanced countries, these are well established but such programs are absent in developing economies.

ii. Disposal in household trash: this should be placed in a sealed plastic bag to prevent them from getting to the environment before they reach the treatment sites.

iii. Flushing of certain medicines. There is a small number of medicines that may be especially harmful and in some cases fatal with just one dose if they are used by some one other than the person for whom the medications was prescribed. To prevent accidental ingestion by children, pets or any other persons, such medicine are flushed down the toilets or sinks as soon as they are no longer needed. However, there should be caution in the application of this disposal method due to current environmental concern of xenobiotics which is still emerging. Usually, medicine recommended for flushing are indicated in the medication guide of such drugs.

4.3. European Union (EU) regulations

The new directive for human pharmaceuticals explicitly requires that all members states should establish collection systems for unused or expired medicines such systems were already in use in several member countries at the time new legislation went into action in 2004. However the directive does not regulate how the collected pharmaceuticals should be handled. Disposal into the sewage system is still the legally accepted route of elimination. However, incineration at high temperature (1200^0C) is a preferred alternative to avoid environmental pollution.

4.4. United States Environmental Protection Agency (EPA) recommendation on disposal of household pharmaceuticals

Many state and local enforcements agencies, communities and organizations have established take back events, mail – back and other collection programs to collect old, expired or simply unwanted prescription and over the counter pharmaceuticals from households. The progress the safe disposal household pharmaceuticals have become more prevalent throughout communities in order to reduce the misuse and abuse of drugs and to prevent the practice of flushing consumer pharmaceuticals which may result in their entry into the environment. There are laws put in place enforced by the Drug Enforcement Administration's (DEA) to protect public health and safety. Many of such drugs are household pharmaceuticals which are collected through the take-back events. In October 2010, the Secure and Responsible Drug Disposal Act of 2010 was enacted. The Act and implementing regulations will provide the basic framework to allow the public who are the ultimate uses to dispose of their unwanted or expired controlled substance pharmaceuticals in a secure and responsible manner. Currently, pharmaceuticals collected from ultimate users in a take back event are mostly destroyed by incineration EPA is currently recommending incineration as the preferred disposal method for household take back programme. Since it is believed that incineration will address both environmental and diversion concerns (EPA 2012). It is an accepted fact that excretion of drugs after human and veterinary therapeutic use dominates the global input of pharmaceuticals

http://dx.doi.org/10.5772/57473

into the environment. Other sources include effluent discharges from hospitals and manufacturing sites if emissions are not properly treated and controlled. If appropriate preventive methods are put in place, disposal of unused drugs can be effectively managed. A drug disposal programme is therefore inevitable and may include guidance for patients, take back schemes and distinct disposal procedures.

Unlike manufacturing related sources and unused drugs, pharmaceutical residues in the environment as a consequence of patients drug use are inevitable. The level of effective sewage treatment in a particular region may reduce the resulting concentrations; but there will still be some residues remaining. Therefore the challenge to scientists and environmentalists is to determine the acceptable level that will pose no significant health risk.

4.5. WHO guideline for safe disposal of unwanted pharmaceuticals

The WHO guidelines on safe disposal of unwanted pharmaceuticals stemmed from experiences of handling large quantities of drugs donated as part of humanitarian assistance during conflicts and natural disasters. Undoubtedly many of the pharmaceuticals save lives and alleviate suffering, but some donations given with good intention may not only be utterly useless but may result in waste and disposal challenges. Pharmaceuticals may arrive past or near their expiry date, may be inappropriate for the needs, be unrecognizable because they are labeled in a foreign language or may have been sent in unwanted quantities. Furthermore, donated pharmaceuticals with a long shelf – life may be mismanaged, particularly in the confusion during and after armed conflict or natural disasters. Staff and storage space may be lacking and the pharmaceutical management system in disarray. Smaller quantities of pharmaceutical waste may accumulate in the absence of emergency situations due to inadequacies in stock management and distribution and to lack of a routine system of disposal. Safe disposal of these unwanted or expired drugs often creates a major problem. To mitigate these challenges, the World Health Organization (WHO) has developed a guidelines for safe disposal of pharmaceutical wastes and unwanted drugs and these include.

a. Disposal methods

- **i.** return to donor or manufacturers
- **ii.** dispatch to landfill
- **iii.** waste immobilization: encapsulation
- **iv.** waste immobilization: inertization
- **v.** dispatch to sewers
- **vi.** Burning in open containers: this can only be used for small quantities to prevent air pollution due to release of smoke and residues.
- **vii.** Medium temperature incineration
- **viii.** Novel high temperature incineration
- **ix.** Chemical decomposition.

b. Sorting

Drugs are better managed when sorted into categories e.g. anti-histamines, expired or unwanted drugs, hazardous or potentially hazardous non-pharmaceutical materials like aerosol cans and recyclable materials.

c. Recommended disposal methods by sorting category sorting leads to application of appropriate disposal methods. For example solids, semi solids and powders, liquids, ampoules, anti-infective drugs, controlled substances, anti-neoplastics, disinfectants and aerosol canisters are disposed differently

4.6. Environmental ethics

The recent identification of single nucleotide polymorphism (SNPs) and their correlation with the modulation of enzyme activity in human cases has further crystallized the links between factors implicated in individual susceptibility and exposure to toxic substances in the environment. The frequently evident opposition between causal interpretations based either on genetic heritage or an external environmental facts serves to focus attention on the possibility that the triumph of "constitutionalist" views may reject the more complex and costly primary prevention measures to deal with pollution. In ethical terms the class between the genetic susceptibility of certain population groups and the vulnerability of the human "condition" bound up with our interdependence on the environment requires that we overcome the prevailing opinion that holds exposure to toxic substances to be normal. The supposed congenital deficient of sore subjects or disorders linked to age, health condition or lifestyles fails to recognize that the risks to human health affect every single person without exception.

Environmental pharmacology or eco-pharmacology, though an evolving scientific concept possesses a great potential to promote "green healthcare", reduce health costs, protect the environment and public health. From all indications environmental-drug contamination from pharmaceutical residues, drug manufacturing, cosmetics, veterinary drugs, and herbicides are of a global concern that calls for drugs environmental fate profiling. Gleaning a lesson from the principle of environmental protection which is prevention, it is important to emphasize prudent drug prescription by physicians. In addition, regulatory agencies should establish functional ecopharmacovigilance programme. This will not only protect the environment but will reduce the evolution of antibiotic stains of pathogens and reduce waste of resources on unused drugs.

4.7. Environmental Risk Assessment (ERA) and environmental classification of drugs

In most developed countries, there are regulatory requirements governing the environmental risk assessment of pharmaceuticals. In most cases, a new regulatory submission or line extension has to be accompanied by an ERA which requires environmental fate and effects tests to be taken (Holm et al 2012). Procedure for ERA involves the generation of a risk quotient; i.e. the ratio of the predicted environmental concentration (PEC) to the predicted no – effect concentration (PNEC) ratio (PEC: PNEC). The PEC provides an estimate of maximum concentration anticipated to occur in the environment resulting from patient use and subse-

http://dx.doi.org/10.5772/57473

quent excretion into the waste water systems. Currently, the concept of ecopharmacovigilance is evolving. This implies environmental protection from pharmaceutical contamination. Although slightly distinct from pharmacovigilance, which is patient oriented, there is nevertheless a measure of provision for ecopharmacovigilance within the European Pharmacovigilance Framework, which includes a reference to the pollution of waters and soils with pharmaceutical residues and states that "member states should consider measures to monitor and evaluate the risk of environmental effects *including those which may have an impact on public health"*.Furthermore, it should be observed that the general industrial practices include environmental impact assessment (EIA) therefore, the concept of ecopharmacovigilance which has drugs, cosmetics and household products as its focus is an additional provision for environment protection

In Sweden, the industry together with universities and health care sector had developed a method for environmental risk assessment and environmental classification of drugs. Environmental risk refers to the risk of toxicity to the aquatic environment. It is based on the ratio between predicted environmental concentration (PEC) and the highest concentration of the substance that does not have a harmful effect in the environment (PNEC). Environmental hazard expresses the inherent environmentally damaging characteristics of the substance in terms of persistence, bioaccumulation and toxicity. The toxicity tests used are usually acute toxicity of fish, acute toxicity of Daphnia specie and growth inhibition test for algae. Most medication on the Swedish market are now classified. This gives the health care practitioner the possibility to make better choices when prescribing medicine (Fent 2006,Daughton and Ruhoy 2008).

5. Ecopharmacovigilance (EPV)

The term "vigilance" according to the dictionary is the ability to maintain attention and alertness over a prolonged period of time. Traditionally, the focus of pharmacovigilance has been directed towards detecting, monitoring collecting, assessing and evaluating data regarding the human hazard posed by medicine, with the primary objective to reduce the occurrence of adverse drug reaction to the patients. While pharmacovigilance has a clinical focus, ecopharmacovigilance has an environmental focus. It will therefore be erroneous to attempt to group the two together. For example, the role of pharmacovigilance commences from post marketing surveillance while ecopharmacovigilance commences from the point of production to the point of disposal. However there is a little provision for environmental protection by those responsible for pharmaco vigilance from unintentional contact with the active ingredient in pharmaceuticals. Therefore as the practice of ecopharmacovigilance evolves, for practical purposes it will be expedient to concede the responsibility to the environmental health or public health department. In an attempt to rightly define the procedure for ecopharmacovigilance, it is important to examine the procedural framework for pharmacovigilance. This include (a) Post marketing surveillance and other methods of adverse drug reactive (ADR) monitoring such as voluntary reporting by doctors (b) dissemination of ADR data through "drug alerts" or "medical alerts" adversaries sent to doctors by pharma-

ceuticals and regulatory agencies such as FDA in the USA, committee on safety of medicines in UK and NAFDAC in Nigeria. (c) Changes in the labeling of medicine indicating restrictions in use or statutory warnings, precautions or even withdrawal of the drug. (Cuklev et al 2012, Fick 2010,Holn et al 2008)

From all indications while pharmacovigilance is patient oriented, ecopharmacovigilance is environment and public health oriented. However, it is rational to have a cooperation between the two. Thus, ecopharmacovigilance can be defined as the "science and activities relating to the safe discharge of effluents from drug manufacturing pants, safe handling and disposal of drugs and syringes in the hospital and sewage plants. While pharmacovigilance falls within the purview of pharmacists, doctors and nurses who deals with administration of drugs, ecopharmacovigilance entails the dedication of environmental health officers, public health engineers, veterinary physicians and agriculturists. However, those to be charged with environmental monitoring of drugs should be knowledgeable in same. In ecopharmacovigilance, there are some practical measures that can be taken to assess environmental risks across the product life-cycle; particularly after the launch of a new drug, to ensure that risk assessment and scientific understanding of pharmaceuticals in the environment remain scientifically and ecologically relevant (Kummerer and Velo 2006,Rahman et al 2007)

These measures include:

a. Ensuring that the effluent from production source are treated and properly disposed of.

b. Tracking environmental risks after launch of the product. If not locally manufactured, via literature monitoring for emerging data on exposure and effects.

c. Using environmental risks management plans, (ERMPs) as a centralized resource to assess and manage the risks of a drug throughout its life cycle.

d. Further research, testing or monitoring in the environment when a risk is identified.

e. Keeping a global EPV perspective

f. Increasing transparency and availability of environmental data for medicinal products.

These measures could help to ensure that any significant environmental issues associated with pharmaceuticals in the environment (PIE) are identified in a timely way and can be managed appropriately (Holn et al 2008).Thus pharmecovigilance should employ a wide spectrum of means to minimize the ecological footprint of medications as well as the possibility of their causing harm to humans and domestic animals, not just by way of intended use, but also by their unintended use as well as cessation of use. Many drugs have double lives. Once the active pharmaceutical ingredients (API) in administered medications have completed their intended purposes in therapy, disease prevention diagnosis or cosmetics, they can take on another lives in the environment. APIs from a large and diverse spectrum of pharmaceuticals can enter the environment as trace contaminants especially in waters, at individual concentrates generally less than a part per billion (mg/l) but sometimes more. The predominant route by which API's gain entry into the environment is via the discharge of treated and untreated sewage contaminate with PAI simply as a result of medications used for the purposes for which they were

http://dx.doi.org/10.5772/57473

designed. Residues of APIs from drugs that are administered parenterally (e.g. via injection and infusion) and entereally (e.g via ingestion) are often excreted in faeces and urine and topically applied medications can be washed from skin during bathing. For most APIs, the fraction of unchanged, parent API transferred to the environment is altered as a result of metabolic activities in the body or transformation within a sewage treatment facility such as microbial degradation, for some APIs, only a small percentage of the total amount used is ever transported to the environment. For others, this percentage can approach 100%.The secondary route of transfer of API to the environment is from the purposed, direct disposal of left over or unwanted medications to sewers as trash (Daughton and Ruhoy 2008).

In ecopharmacovigilance, pharmacovigilance and environmental protection are intimately tied just as are human health and ecological integrity (Daughton 2003a). The importance of ecopharmacovigilance cannot be over emphasized and if properly applied, there will be reduction in ecological exposure to drug contaminants and reduction of drug residues though at low levels making their way into our food and drinking water supplies, thereby further reducing human exposure. The ultimate goal of ecopharmaco vigilance should be the design and implementation of changes in the aspects of the drug distribution/consumption chain in order to minimize or eliminate the generation of left over medications so that disposal is not needed to begin with. Ecopharmacovigilance has the potential to influence the re-designing of the healthcare system so that only the most efficacious medications are presented in minimal doses and dispersed in quantities and for durations to ensure their full consumption. The ideal outcome would be the absence of left over drugs which require disposal. EPV also promotes the concept of "greener" healthcare system which not only protects the environment but ensure more official utilization of healthcare resources, reduced healthcare costs, improved healthcare outcome and reduced incidence of purposeful drug abuse and accidental poisonings from diversion of stock piled drugs.

6. Discussion

Drugs and house hold products are part of man's needs for various purposes. Drugs are prescribed for various medical conditions and cosmetics and house hold products are consumables of daily need. However, there is a growing concern among scientists and environmentalists on the impact of drug contaminants on the environment. This phenomenon is not limited to any region of the world but global. In many countries, low levels of medicines have been detected in sewage treatment plant (STP), effluents, surface water, ground water and drinking water. Effects of some drugs have been investigated in aquatic ecosystems and different species of the aquatic environment are known to be affected by disposed drugs when present.

The dramatic decline in vulture population in Asia which was linked to the use of diclofenac to treat cattle is a classical case of the importance of ecopharmacology. An alarming decline in the number of vultures poses the threat of outbreak of epidemics in parts of Asia due to potential increase in the number of decaying carcasses as a result of this. The three species of

Asia vultures viz Asian white-backed vultures, (*Gyps bengalensis*) Indian vultures (*Gyps indicus)* and slender-billed vultures (*Gyps tenuirostris)* are listed as critically endangered by the International Union of Conservation of Nature (IUCN) based in Switzerland. Furthermore, the decline in the vulture population has threatened the tradition of "Parsis"; a sect of the Zoroastians who traditionally expose human corpses to vultures for disposal. As a sequelae in Mumbia, India, it had been reported that Parsis have stopped leaving human corpses in the "Tower of Silence" because the vultures that once quickly consumed the carcasses are vanishing (Houston 1990).

There have been specific cases of intersex fish in European rivers. The fact that traces of different drugs and personal care products including steroids and insect repellant have been detected in the American waters and the fact that traces of cocaine have been detected in River Thames in London underscores the global dimension of environmental drugs contamination. In India, different studies have shown that effluent from waste water treatment plant serving several pharmaceutical companies contain residues of many drugs, particularly antibiotics. However, it is generally accepted that the major sources of release of drugs to the ecosystem is from treated and untreated sewage end products due to human consumption and disposal of drugs. An important factor that promotes the release of pharmaceutical and house products into the environment is decaying infrastructure whereby aging sewage pipes are cause leaks of effluents into the environment.

Perhaps another area of neglect currently in ecopharmacology is the potential effect of herbal preparations. Herbal drugs have pharmacological properties which are likely to be ignored with respect to their environmental impact due to the assumption that plants are generally natural entities and therefore environmentally friendly. There is therefore the necessity for more studies of environmental impact of herbarium processes. In the same respect the effect of marijuana" probably the most commonly consumed narcotic worldwide on the ecosystem is likely to be dramatic. For example, it was observed that hay contaminated with the Chinese herb *Aristolochia* specie caused renal failure in horses (Grollman 2013). In addition, Parsley; another commonly used herbal preparation was said to have the negative attribute of absorbing toxic metals from the environment and therefore, its cultivation near waste water or using waste water for its irrigation is discouraged (Awe and Banjoko 2012). It is also important to note that preventing environmental drug contamination will protect the very important biofilm of the ecosystem and of the sewage system for proper functioning. The basic principle of environmental protection is prevention of environmental pollution, minimizing unavoidable emissions and remediating any existing damage. With reference to environmental pharmacology, it is therefore expedient to reduce as much as possible the use and circulation of drugs and establish a program or coordinated disposal of unused drugs. For example, there could be a take-back scheme whereby unused drugs are returned to the source of dispensing for proper disposal. There should be more prudent prescribing of drugs and patient use. Private stock piling of drugs and improper storage should be discouraged and the established drug disposal route should be monitored periodically. The very important impact of unsafe disposal of drugs is the potential of promoting the evolution of antimicrobial resistant

http://dx.doi.org/10.5772/57473

pathogens. This has a significant impact on clinical practice, public health, health economics and even ecopharmacology.

7. Conclusion and recommendations

The scope of human exposure to pharmaceuticals and personal care products from the environment is a complex function of many factors. These factors include the concentrations, types and distribution of pharmaceuticals in the environment, the pharmacokinetics is of each drug, the structural transformation of the chemical compounds either through metabolism or natural degradation processes and the potential bioaccumulation of the drugs. Furthermore, the full effects of mixtures of low concentrations of different PPCPs is also unknown there is therefore concern about the potential they have for harm because they may act unpredictably when mixed with other chemicals from the environment or concentration in the food chain. In addition,, some PPCPS are active at very low concentrations, and are often released continuously in large or widespread quantities. Proper destruction of pharmaceutical residues should yield rest products without any environmental formation of such new products. Incineration at a high temperature greater then 1000 degrees Celsius is considered to fulfill the requirements, but even following such incineration residual ashes from the incineration should be properly taken care of. Pharmaceuticals used in veterinary medicine or as additives to animal food, pose a different problem, since they are excreted into soil or possibly open surface waters. It is well known that such excretions may affect terrestrial organisms directly, leading to extinction of exposed species e.g. dung beetles. Futhermore, lipid – soluble pharma residues from veterinary use may bind strongly to soil particles, with little tendency to leak out to ground water or to local surface waters. In addition more water – soluble residues may be washed out with rain or melting snow and reach both ground water and surface water streams.

8. Recommendations

- Contamination of drinking water mist be avoided and landfills must be sited and constructed in a way that minimizes the possibility of leachate entering an aquifer, surface water or drinking water system.
- Non- biodegradable drugs, antibiotics, anti-neoplastics and disinfectants should not be disposed into the sewage system as they may kill bacteria necessary for the treatment of sewage. Anti-neoplastics should not be flushed into water courses as they may damage aquatic life or contaminate drinking water. Similarly, large quantities of disinfectants should not be discharged into sewerage system or water course but can be introduced if well diluted.
- Burning pharmaceuticals at low temperature or in open containers results in release of toxic pollutants into the air. Ideally this should be avoided.

- Inefficient and insecure sorting and disposal may allow drugs beyond their expiry date to be diverted for resale to the general public. In some countries, scavenging in unprotected insecure landfills is a hazard.
- In the absence of suitable disposal sites and qualified personnel to supervise disposal, unwanted pharmaceuticals present no risk provided they are securely stored in dry conditions. If stored in their original packing, there is a risk of diversion and to avoid this, they are best stored in drins with the pharmaceuticals immobilized.
- Effective environmental detection methods have to be developed and global detection strategy applied to map the current global situation.
- There are currently no test methods to assess whether negative effects may occur after long term environmental diffuse exposure in humans, during the vulnerable periods of development, on aquatic micro organisms or how it may affect other animals. Therefore the precautionary principle must be guiding.
- Concentrations in surface water alone are not sufficient to assess the risk of negative environmental effects of these synthetic chemicals. Consideration must be taken to bioaccumulation in fish and other aquatic foods consumed by humans, as well as to additive and synergistic effects between pharmaceuticals and other chemicals in the contaminated wate

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