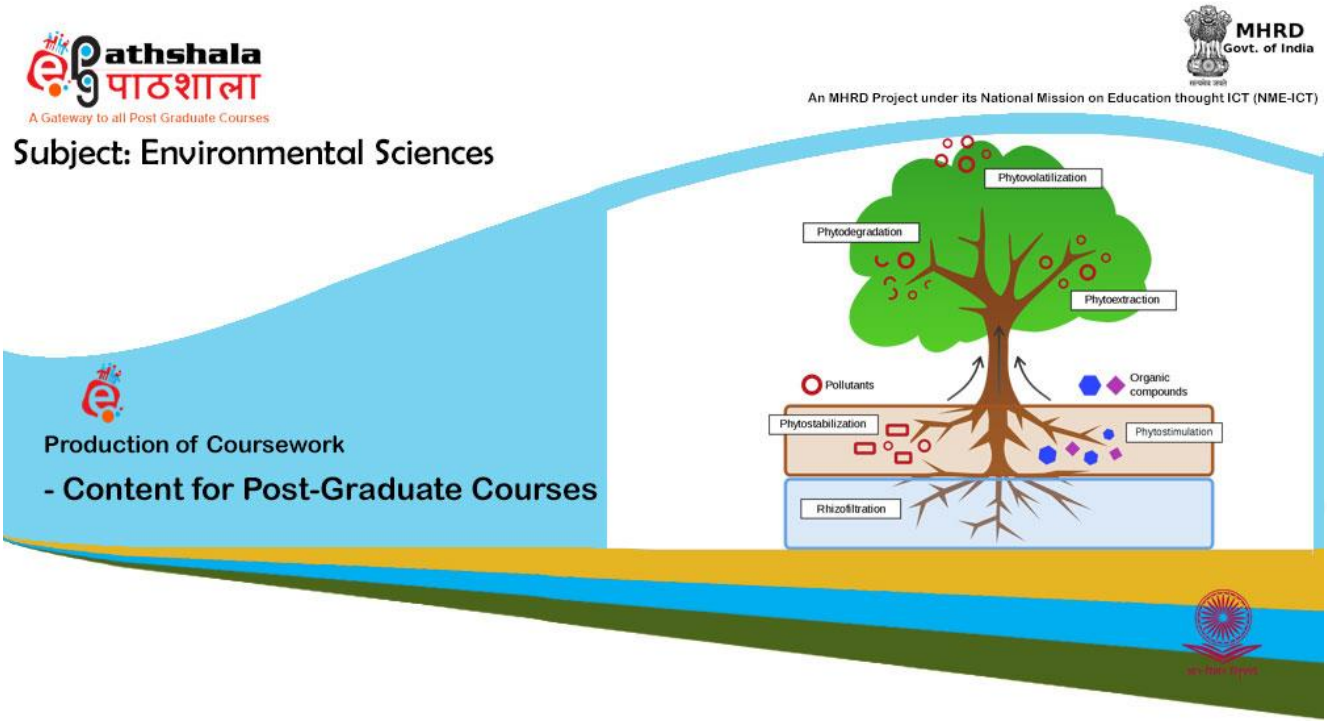

Paper No: 15 **Environmental Microbiology & Biotechnology**

Module: 32 Xenobiotics

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Description of Module	
Subject Name	**Environmental Sciences**
Paper Name	Environmental Microbiology & Biotechnology
Module Name/Title	**Xenobiotics**
Module Id	EVS/EMB-XV/32
Pre-requisites	Basic Knowledge of chemistry and biology
Objectives	To learn about xenobiotics, their properties and structural features, mechanism of biodegradation
Keywords	Xenobiotics, PCBc, Halocarbons, biodegradation

Module 32 : Xenobiotics

Content

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Xenobiotics: Xenobiotic (Greek, xenos "foreign"; bios "life"). Xenobiotics are manmade substances that are foreign to complete biological system which are not generated by the body itself and did not exist previously before they were generated synthetically by humans (Sharma et. al. 2016). Likewise, the substances if present in higher concentration than usual are also grouped under xenobiotics. Xenobiotics are any chemical/synthetic complexes that are found in any living organism but are unknown to that organism as it does not usually produce the compound or consume it as a part of its diet. For example, the fish that live downstream from the outlet of the sewage treatment plant are affected mostly. Hormones produced by humans may be present in the water and for fish they are foreign compounds (Llorca et. al. 2016).

Properties of xenobiotic compounds (Foti and Dalvie 2016):

1. They are extremely stable in nature and insoluble in water.
2. Degradative microorganisms do not recognize them as substrate.
3. They are extremely toxic and contain large molecular weight that checks entrance into microbial cells.

Structural features of xenobiotic compounds:

1. Instead of hydrogen, halogen is present in the molecule which needs additional energy for cleavage.
2. Other groups like sulphonate, nitro, amino, methoxy, etc. are present.
3. Cycloalkanes, aromatic compounds, and heterocyclic compounds are more recalcitrant.
4. Branched linear chains are resistant to biodegradation.

Kinds of recalcitrant xenobiotics (Szöllősi et. al. 2016**):**

They are basically categorized into six types:

1. **Halocarbons:** These xenobiotic compounds contain halogens in diverse amounts viz. chlorine, bromine, fluorine or iodine instead of hydrogen atoms. They find their application in various ways such as propellants in spray cans of cosmetics, paints etc., and solvents such as chloroform. They are also used in condenser units of cooling systems (freons, CCl_3F, CCl_2F_2 etc.) and as insecticide (DDT, BHC, lindane etc.) and herbicide such as dalapon (Jha et. al.

2015). Chloroform and freons which are basically volatile in nature and released into the atmosphere where they devastate protective ozone layer that leads to increased UV radiation.

2. **Polychlorinated biphenyls (PCBs):** These complexes are covalently linked with two benzene rings have halogen in place of hydrogen. They are basically utilized as coolants in transformer or as exchange fluids for heat (Bonde et. al. 2016).
3. **Synthetic polymers:** These are polyethylene, polyvinyl chloride, polystyrene, etc., and nylons, which are used as article of clothing, enveloping material etc. They are recalcitrant because they are extremely insoluble in water and their molecular size.
4. **Alkylbenzyl Sulphonates**: They are surface-active detergents that are superior as compared to soaps. The sulphonate (-SO_3-) group at one end opposes microbial degradation, while the other end becomes recalcitrant if it is branched. Degree of resistance increase with the increase in branch length. In the present scenario, alkylbenzyl sulphonates having non branched alkyl ends are utilized as they are bio-degraded by beta oxidation from their alkyl ends (Jha et. al. 2015).
5. **Oil Mixtures**: Oil is recalcitrant basically because it is not soluble in water and due to lethal nature of some of its compounds. It is naturally produced that contains many components which are biodegradable in nature. Biodegradation is used when there is small oil seepage but when large spill occurs these complexes are recalcitrant in nature (Kumrungsee et. al. 2014).
6. **Other xenobiotics**: Compounds containing aliphatic, cyclic ring arrangements that contains nitro, sulphonates, amino, methoxy, or carbamyl groups other than halogen group. These properties make them recalcitrant.

Xenobiotic compound find many application in our day to day lives such as food additives, drugs or pesticides. On the other hand they are harmful towards nature and health as environmental pollutants like dioxins, furans and carcinogen. Because of which xenobiotics are employed in this context very often (Srivastava et. al. 2016).

Biodegradation:

Microorganisms on introduction to xenobiotics build up the capability to degrade the same like mutations. Mutation results in modifications of gene in microorganisms in order that the active site of enzyme is altered to show enhanced affinity for xenobiotics. Definite mutations may also result in developing novel enzyme pathway so as to degrade xenobiotics. Usually mixture of microorganisms is

suggested as it is being examined that they give in faster end results. This is because two dissimilar types of microorganisms attack two dissimilar parts in the course of dissimilar mechanisms which results in effective breakdown. This also builds a state of co-metabolism. The amendment in definite genes of microorganisms to facilitate breakdown xenobiotics is highly proposed and is observed to generate high precision. Some xenobiotic compounds are degraded by photochemical disintegration which has been proposed as a considerable way of degradation (Hirahara *et al.*, 2001).

The most general requirement for biodegrading xenobiotics is summarized below:

1. Availability of xenobiotic complex to microbes: Compounds may possibly be adsorbed to particular matter available in soil biome, therefore prevent prospective attack from microbes. Likewise, chemical complexes with additional molecules may direct to give similar outcome (Taguer and Maurice 2016).

2. Entrance of a compound into an organism: Absence of suitable extracellular enzymes and lack of penetration results in compound being resistant to biological degradation. In order to facilitate the entry of natural compounds definite transport mechanisms have been evolved (Wu et. al. 2014). Yet, on initial contact to xenobiotic complex the uptake mechanism is suspicious to function.

3. Stimulation of catabolic enzymes: The xenobiotic complex should work as substrate or induce the synthesis of degradative enzymes. Xenobiotic halo-organic complexes are incapable to utilize as feedstock for microorganisms because they are eliminated from conventional catabolic pathways. Accordingly, xenobiotic compound is not able to convert to transitional compound that could be mineralized further in already prevailing biochemical pathway (Gianfreda et. al. 2016). Substitution by halogen sufficiently changes a molecule structure with the aim to curtail the rapidity of transformation, and may possibly check its metabolism. As for example, to some point the providence of xenobiotics is verified through degree of structural analogy amid the natural and man-made composites in support of which catabolic function subsist (**Fig. 1**). These structural similarities contain analogous reactivities, in conjunction with comparable magnitude and polarization of functional groups (Allendorf and Stavila 2015).

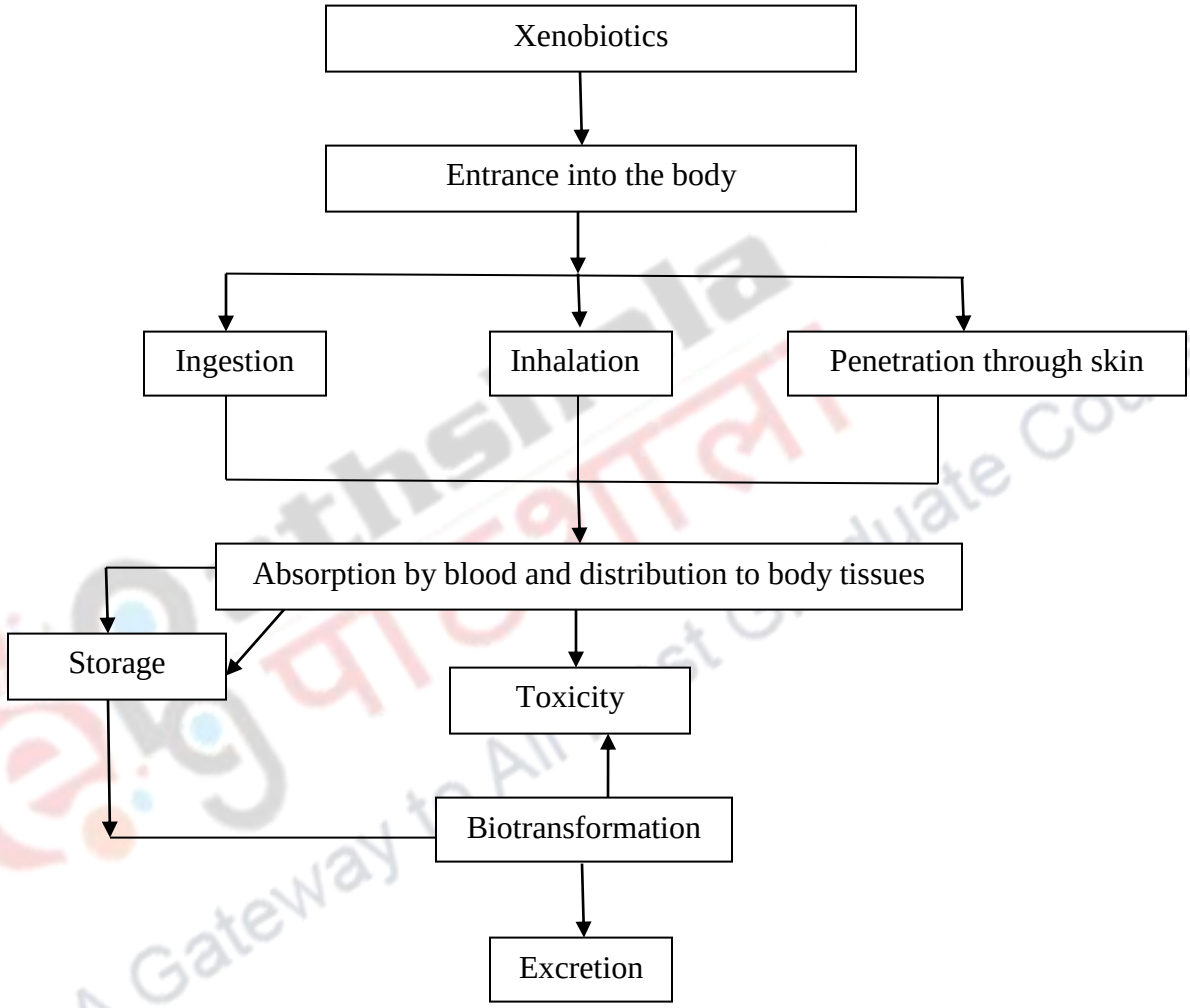
Xenobiotics
Entrance into the body
Ingestion
Inhalation
Penetration through skin
Absorption by blood and distribution to body tissues
Storage
Toxicity
Biotransformation
Excretion

Fig : 1

4. Aerobic or anaerobic surroundings: Aerobic or anoxic environment be able to build up few complexes that could be degraded by different conditions (Alexander, 1981).

Mechanisms for biodegradation of xenobiotics

These compounds, for the reason that they are recalcitrant in nature, are very difficult to breakdown and degrade. The complexities in its chemical composition aggravate the problem. In order to breakdown such compounds, enzymes act on few groups as for example within the halocarbon group, halogen grouping is attacked. Enzymes such as oxygenases take part in a foremost function. Chemical bonds such as ester-, ether- bonds or amide- that exists in the complexes are attacked initially leads to splitting of complexes (Tiwari et. al. 2017). In another cases aliphatic chains or aromatic constituents may be aimed accordingly. Mode and site of intrusion rests solely upon the enzymatic exploitation, their concentration and favorable situations. Frequently it is observed that these compounds doesn't utilize it as a basis of energy; therefore are not degraded (Kassotaki et. al. 2016). In order to induce breakdown of these compounds certain substances are added and the procedure of degeneration is called as **co-metabolism**. While in one more progression, the xenobiotic complexes act as feedstocks as well as are utilized to discharge energy. This process is known as **gratuitous metabolism (**Mathews and Sithebe 2015**).**

For halo-organo compounds three most important biodegradative mechanisms have been accounted. In the end, mineralization or complete degradation of compound is to be achieved, so as to prevent its persistent nature (Magureanu et. al. 2015). It involves absolute disintegration of organic complex converted to inert nature furthermore in end the alteration of carbon skeleton into mediator products or metabolites.

A subsequent method comprises incomplete disintegration that is undoubtedly depicted by halo-aromatic complexes. As for instance, PCB's are constituted by pair of aromatic ring that possibly will contain unsubstituted and one chloro-substituted ring (Forrest et. al. 2014). Sometimes an organism can utilize the unsubstituted nucleus as the growth substrate, whereas the halo- substituted ring will be excreted into the culture fluid as an end product.

Co-metabolism is the third type of mechanism that alters the structure of the chemical without extracting the energy from the catabolism for the growth of microorganisms (Jha et. al. 2015). The population of microorganisms that are implicated in co-metabolism is supposed to nurture on added feedstock whilst transforming the xenobiotic compound. Incapability of the co-metabolizing microbes to use the compound is reflected by the lack of boost in population biomass. Co-metabolism of halo-organic compounds does not end in complete mineralization to carbon dioxide, water or inorganic halide, but it significantly reduce toxicity in the atmosphere (Nagarajan 2014). This indicated the ecological importance of this type of mechanisms. It has been recommended that co-metabolism may be accounted for the degradation of many xenobiotic compounds that do not sustain microbial growth (Passatore et. al. 2014). Compounds for instance 1, 1, 1-trichloro-2, 2-bis (p-chlorophenyl) ethane and other similar particles are studied comprehensively (Ouyang et. al. 2014). In few other cases, complete mineralization doesn't occur but the noxious consequence of the xenobiotic complex was reduced.

However, the huge numbers of xenobiotic composites are actually co-metabolized, that establishes a physiological explanation which is quite important (El-Naas et. al. 2014). The accepted supposition is related to enzyme distinctively. Numerous of the enzymes that exist in microbial cells catalyze reactions that involve several dissimilar but chemically related feedstocks. These enzymes are of wide feedstock specificities. Therefore, the end product formed from such chemically related compounds prevents further mineralization in addition to production of energy for microbial augmentation. This implies with the purpose that toxicity of a compound is lessened to some extent but not completely removed by co-metabolism.

Biotransformation of Xenobiotics: Biotransformation reaction occurs by two phases of reactions (Bussy et. al. 2014) that are discussed below:

1. Phase I Reactions: Phase I reaction alters the xenobiotic complex from lipophilic to polar so as to commence individual groups into the preliminary compound: -OH, -NH2, -COOH, or –SH (Kennedy and Tierney 2013). This reaction involves following reactions:

1.1. Oxidation; Monooxygenation (main Rx): **For example:**

Benzene - (aromatic hydroxylation) ⟶ epoxide. Then any of two probable reactions takes place:

(a) epoxide -(non enzymatic rearrangement)⟶ phenol

(b) epoxide -(epoxide hydrolyase) ⟶ 1,2-dihydro-1,2-diol

also 1,2-dihydro-1,2-diol -(cytosolic dehydrogenase) ⟶ catechol

***1.2. Reduction; azo/ nitro compounds*:** It is supported by anaerobic conditions that most commonly take place in mammalian tissue wherever oxygen concentration is short. However, air or oxygen is replaced with nitrogen in in-vitro conditions (Berenbaum et. al. 2015). Nitro reduction (nitro reductase) and azo reduction (azo reductase) are the two types of reductions (Mercier et. al. 2013) in which nitro reduction involves three chief enzyme systems that are

(a) Cytochrome P450 (e.g., in liver). Hindered by CO (Zanger and Schwab 2013)

(b) DT-diaphorase: cytosolic flavoprotein (in liver) = NAD(P)H quinone oxido reductase

(c) Bacterial intestinal enzymes

***1.3. Hydrolysis; esters*:** Substrates that are involved in hydrolysis are:

(a) phosphate ester

(b) carboxylic acid ester, amides

(c) epoxide

Whereas, the enzymes that are utilized are epoxide hydrolase. Most of the enzymes are in microsomes or in cytosol. While the product formed at the end is always trans hydroxyls.

2. Phase II Reactions: Phase I metabolites or parent xenobiotic compound which contains appropriate reactions go through conjugation reactions amid the substrates to capitulate conjugates. Basically, conjugates are polar in nature which is readily excreted. Different types of phase II reactions (Gao et. al. 2014) are described in **Table No. 1** as well as below:

2.1 Glucuronidation: Its reaction distinctiveness is low attraction, high capability for catalysis and availability of proficient feedstock conjugation at high substrate concentrations. The enzyme that is utilized for glucuronidation is UDP glucuronosyl transferases (UGT) which are results of a multigene superfamily (Bozzolan et. al. 2014).

***.2.2. Sulfation*:** The main reaction characteristics are high-affinity, little capability for catalysis and availability of competent feedstock conjugation at low concentrations. Sulfate is speed restraining constituent inside cells. Entire amount of sulfation is enhanced by incorporating sulfate (or methionine or cysteines which break down into inorganic sulfate). The enzymes utilized in sulfations are superfamily of enzymes (Chen et. al. 2015). Most important subfamilies of cytosolic sulfotransferases

are included as SULT L SULT 2 and SULT 3. The end product released after sulfate conjugation entails the relocation of sulfonate (SO_3-), not sulfate (SO_4-) from phosphoadenosinephosphosulfate (PAPS) to the xenobiotic (Hudson et. al. 2014)

2.3. Glutathione conjugation: Substrates that are involved in glutathione conjugation comprises an vast array of electrophilic xenobiotics, otherwise xenobiotics biotransformed into electrophiles. To act as substrates for glutathione S-transferase (GST), the compound should exhibit three general features 1) hydrophobic; 2) electrophilic; 3) react non enzymatically with glutathione (GSH) at a computable rate. Also, the quantity of GSH is extremely high in liver (10 mM) along with GST that makes up 10% of overall cellular protein. GSH is the co-factor for GST (Orellana et. al. 2015).

2.4. Acetylation: Two types of acetylation reactions take place. One engaged xenobiotic compound and an activated conjugating intermediate, acetyl CoA. This reaction is called as acetylation (Kennedy and Tierney 2013). The other type of reaction involves xenobiotic compound and a derivative of actyl CoA, which responds with every amino acid to make an amino acid conjugate. The reaction in acetylation, normally results in masking of amino collection by means of a non-ionizable acetyl moiety. Because of which, the acetylated derives are usually less water soluble as compared to the parent composite. Enzymes involved in acetylation are two cytoplasmic N-acetyltransferases, NAT1 and NAT2 are found in human beings (Bejrowska et. al. 2015). A third enzyme, NAT3, is found in mice.

2.5. Methylation: Methylation is an ordinary but usually an insignificant pathway of xenobiotic metabolism (Gao et. al. 2014). A methylation phase II reaction usually reduce the water solubility of xenobiotics compounds and covers functional groups or else are conjugated by other phase II enzymes. Nevertheless, methylation responses that generate quaternary ammonium ions or methylation to facilitate generation of positively charged sulfonium ions which increase the solubility (Palmer et. al. 2014).

Table 1: Summary of Phase II Reactions

S.No.	Type of Conjugation	Endogenous Reactant	Reactive site	Types of Substrates	Examples
1.	Glucoronidation	UDP Glucuronic Acid	OH,COOH, NH_2, SH, C-C	Phenols, Alcohols, carboxylic acids, hydroxylamine	Acetaminophen, nitrophenol
2.	Sulfation	Phosoadenosyl phosphosulfate	NH_2, OH	Phenols, Alcohols, Aromatic amines	Aniline, phenol, acetaminophen
3.	Acetylation	Acetyl-CoA	NH_2, SO_2NH_2 OH	Amines	Isoniazid, sulfonamide
4.	Methylation	S-adenosyl-methionine	NH_2, OH, SH	Phenols, amines, catecholamines	Pyridine, histamine, epinephrine
5.	Amino acid conjugation	Glycine	COOH	Acetyl CoA derivatives of carboxylic acid.	-

The main purpose of these two phases for metabolizing xenobiotics is to augment their polarity (water solubility) so as to facilitate their excretion from human body. Since, extremely hydrophobic xenobiotics would remain in adipose tissues nearly indefinitely if not converted to polar nature therefore will cause threat to environment.

Hazards caused by xenobiotic compounds

Xenobiotic compound pose huge environmental hazards. They are extremely toxic in nature and have an effect on continued existence of lower as well as higher eukaryotes. They are identified to cause health hazards to mankind in various ways like skin problems, disrupt reproductive system and even may be the cause of triggering cancer. These compounds have the property of bioaccumulation or biomagnifications as they are continual and stay in the atmosphere for numerous years. They are also found in food chains and the concentration was established to be exceptionally high in organisms that are not in direct touch with xenobiotics (Morris et. al. 2016). The threats caused by xenobiotics are discussed in detail:

Effects on aquatic ecosystem:

Aquatic organisms are particularly important targets, as they are exposed through wastewater residues over their entire life. Fent et al. (2006) reviewed and compiled the environmental occurrence and outcome of human being pharmaceuticals in the marine environment, discussed potential mechanisms of action based on knowledge from mammalian experiments, and described the acute and chronic eco-toxicological effects on aquatic organisms. Pharmaceuticals after their application in their indigenous form are excreted or else as metabolites and penetrate marine life through diverse pathways. The major route in human is ingestion then excretion and disposed of through waste water. That main route for bringing human pharmaceuticals and unused medicines in the aquatic environment is waste water after disposal. Likewise, wastewater from hospitals, leachates from landfills or wastewater from manufacturers' contains considerable amount of xenobiotics. They may also enter marine system through fertilizer application in fields and then through runoff or they are directly applied during fish farming (Burkina et al. 2015).

Egg-shell thinning of birds through DDE (DichloroDiphenylDichloro Ethylene) perhaps the very good example of reproductive deficiency leading the deteriorations of voluminous populations in a several raptor species in Europe and North America (Lundholm 1997).

In the induction of ovotestisin male western gulls, the developmental exposurehas been formerly linkedto the DDT complex (DiChloroDiphenylTrichloro Ethane).

EDCs (Endocrine disruptors) harmfully affect the fish population as for instance effluents from waste water treatment plants or from the extremepolluted areas are generally linked to the effects on reproduction pattern of the fish population. Same way turtles are also affected (Cleuvers, 2003).

Effects on plants:

The worldwide enhancement in the influence of herbal drugs demandspharmacological attributes of the botanical plants should be handled carefully to avoid the contamination in the surface water, vegetables and crops. The most common herb that contaminates the ecological ecosystem is marijiuana that has the capability to interfere the biological system of flora and other fauna. Marijiuana is the most typical herb that contaminates ecological system and has capability to affect the genetic structure of the fauna and flora. St. John's wort studied on this herb the reason of modulation of Cytochrome P450 and possibility of the hampering with approved therapeutic agents (Guegenrich, 1997). Aristolochic Acid (AA) is an innate composite generally present in several plants of the Aristolochiagenius.

During 1990s, examining of epidemiological has shown AA contact was linked through an elevated threat of nephrotoxicity and upper urinary tract urothelial cell carcinoma (UTUC) (Grollman et al. 2007; Debelle et al. 2008).This is initiated due to the capability of AA to fix with DNA, that forms DNA adduct (Arlt et. al. 2002). Consequences of these lead to prohibition on the application of Aristolochiawhich contains herbal provisionsfrom 2001 in Europe and North America and since 2003 in Asia (Debelle et al. 2008).

Effects on humans:

The mankind got exposed to the endocrine disruptors, the most likely pathway involve through direct exposure at work place, and via consumer products for instance food, paints, detergents and cosmetics in addition to indirect exposure through the atmosphere, viz air, water and soil.

Apart from the drug DES (synthetic oestrogens), environmental oestrogens are never been proven to create human health troubles (Klatte et. al. 2016).

Lead is known to be hepatotoxic while cadmium is a well-known nephrotoxic agent (Matović et. al. 2015). Symptoms of pesticide toxicity include headache, dizziness, muscular weakness and nausea. Chronic exposure to several xenobiotics cause damage to the liver, kidneys, and nervous systems (Singh et. al. 2016) together with the active and inert components in pesticides can be organic compounds; thus, together they could append to the levels of airborne organics (Sarwar 2015).

Bisphenol A, a constituent utilized in many plastic manufactured goods binds to the local anaesthetic receptor site to block the human cardiac sodium channel (Embrandiri et. al. 2016). There are currently recognized links between EDC and some female diseases and pelvic inflammatory diseases. Other includes osteoporosis, foetal growth, precocious puberty, child development, and obesity (Meeker, 2014).

Conclusions

With the increase in population and urbanization, there is more likelihood of the contamination of xenobiotics in food and water we consume. Although there are many detection methods and sewage treatment techniques, xenobiotics is rapidly becoming a threat to the ecosystem as over long term there is constrained to be repercussions. From our each day care merchandises to agricultural utilized the presence of destructive xenobiotics is been detected. Long term effects are autoimmune disorders, cardiac problems and ultimately cancer due to the extended utilization of these contaminants in food or drinks. It is consequently an immense challenge to the environment wellbeing researchers to deal with this matter. Studies are on-going with regard to antibiotic resistance in sewage as the existing trend will direct towards a worldwide disaster. The earlier remedies or defensive techniques are put in place, the enhanced it is for the natural ecosystem.

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