Editorial

Dangers of Xenobiotics To Health and Ecosystem

Doi: https://doi.org/10.3329/kyamcj.v13i4.64927

The word 'xenobiotic' is a derivative of Greek words 'xenos' (meaning foreign/foreigner or strange/stranger) and 'bios' (meaning life/of life/pertaining to life). Thus, 'xenobiotics' stand for substances alien or detrimental to life of organisms. The first known use of the term of xenobiotic was in 1965. Human exposure to xenobiotics dates back to the pre-historical period. But interest in xenobiotics metabolism & excretion dates from only the mid-19th century as the technique and knowledge of biochemistry were then first applied to explore into the depth. Thereafter for about one hundred years, biotransformation of toxic foreign substances was in general equation with detoxification and the excretion or elimination of the noxious agents. During the 1970s, under the auspices of non-profit prestigious GRC (Gordon Research Conference) on Drug Metabolism took a courageous step to organize an international society to promote the interaction of scientists (of basic pharmacology, biochemistry, toxicology, and oncology) dedicated exclusively to study the effects of xenobiotics in living beings. In 1981, the premier scientific body called the ISSX (International Society for the Study of the Xenobiotics) was formed. The ISSX has now strong international foundation comprising several thousand members from over fifty countries. Their International conferences are held once in every three years. The ISSX now holds multiple regional meetings and workshops in Europe, Asia/Pacific & North America on regular basis. Bangladesh is a designated country eligible for membership of ISSX as noted in the World Bank Website for the 2021 fiscal year. But no more information is available regarding the membership of Bangladesh for the 2022 fiscal year.[1,2]

Now as the current era of fourth industrial revolution of Internet, Renewable Energy, Robotics, Virtual Reality and Artificial Intelligence is advancing rapidly over the first (Coal, 1765), the second (Gas, 1870) and the third (Electronics & Nuclear Energy, 1969) industrial revolutions, xenobiotics are equally drawing our attention to protect the humans and the circum-ambient ecosystems. Because they are being increasingly produced, equally increasingly threatening the life of all living beings, more importantly the life of humans and the human habitation. Man-made exogenous xenobiotics are drawing our attention more. But some endogenous byproducts of our metabolism have effects similar to those of exogenous xenobiotics. These endogenous toxic chemicals include bilirubin, bile acids and their salts, certain steroids, eicosanoids and certain fatty acids. Now the term 'xenobiotic' is used as a general term for hazardous exogenous chemicals, both elementary and compound, which are non-nutrients for animal use, and that gets entry into the living system and their food plus metabolic chains via such pathways as contamination, inhalation, ingestion, absorption, diffusion, osmosis etc. An exogenous xenobiotic is not occurring normally in the metabolic pathways of a biological system. Xenobiotics with potential carcinogenic activity can be generated from meat and fish components through some cooking procedures at high temperatures. Medicinal preparations are well-known xenobiotics. Plant products, drugs, antioxidants, insecticides, pesticides, cosmetics, flavoring agents, perfumes and other fragrant chemicals, food additives, food supplements, alcohols (other than ethanol), hydrocarbons, synthetic polymers, oil mixtures, industrial effluents and chemicals, heavy metals, smokes, exhaust fumes, other noxious gases and many other occupational and environmental contaminants are now universally taken together as exogenous xenobiotics which are dangerously detrimental to humans and the ecosystems. Most of these xenobiotics are man-made substances that are present in the environment at unnaturally high concentrations. A negligible amount of xenobiotics are produced at much lower concentrations in nature. When some naturally available substances called the endobiotics are found in high and excessive concentrations, they can become detrimental like exogenous xenobiotics. Some natural compounds when are taken up by another organism, such as the uptake of natural human hormones by fish found in downstream of sewerage treatment plant outfalls, or the defensive chemicals (like mycotoxins, bacterial and herbal toxins etc.) generated by some organisms against predators can act as xenobiotics. As exogenous xenobiotics are omnipresent, human exposure to them are unavoidable. Exposure to medicinal and remedial xenobiotics are voluntary as they are being taken for their presumptive beneficial effects upon health and life. These include drugs, antibiotics, food additive, food supplements, spices and antioxidants etc. Recalcitrant xenobiotics resist biodegradation and persist in the environment for long period of time. Many such xenobiotics as plastics and pesticides are carcinogenic and mutagenic, with serious health hazards extending over several generations. Chromatographic analysis is used to separate xenobiotics from and detect in other compounds found in air, soil, surface waters, sludges, other ground matrices, foods and food products, food additives and in human and veterinary health care products.[1,3]

The chargeless highly reactive, flammable, soft, silvery-white alkali metal lithium is the simplest form of elemental xenobiotic. But this lithium is approved for human use in psychiatric bipolar disorder that improves longevity (life-span) and health-span. This is an example of exceptional health benefit from a xenobiotic like many other useful drugs (medicinal preparations). Though these drugs like lithium can cause renal, thyroid, cardiac and many other innumerable health problems. FA (Formaldehyde) gas is an omnipresent air pollutant xenobiotic that is being extensive exposed to humans. Ethyl alcohol (Ethanol) is not typically regarded as a xenobiotic. It is metabolized mainly in the liver by alcohol dehydrogenase (ADH) producing acetaldehyde. CYP2E1 (Cytochrome P450 2E1) is involved to produce acetaldehyde when alcohol load is high. The liver breaks ethanol ultimately into ketones at a rate of

about 0.015 g/100mL/hour, reducing Blood Alcohol Content (BAC) by 0.015 per hour. A BAC of 0.10 by mass i.e., 0.10% is 0.10 g of alcohol per 100 g of blood (23 mmol/L). A BAC of 0.0 is accepted as sober (not intoxicated). Though the liver is the principal organ to detoxify ethanol, the brain, the pancreas, and the stomach can also metabolize alcohol. Many heavy drinkers do not get malignant diseases, and some moderate drinkers get malignancy in their life-time. Glucocorticoids including almost all other corticosteroids are potent anti-inflammatory substances that are utilized to treat SLE (Systemic Lupus Erythematosus), RA (Rheumatoid Arthritis), BA (Bronchial Asthma), GD (Crohn's Disease) and many other different types of allergies. After absorption, caffeine is quickly distributed to most tissues and body fluids including bile, milk, saliva, semen, sweat, and urine, although it is received in the body as a xenobiotic substance. Caffeine is ultimately broken down (metabolized) in the liver into three major metabolites: paraxanthine (84%), theobromine (12%), and theophylline (4%). All these three metabolites are also active ingredients. Following metabolism in the liver, the kidneys excrete the caffeine, that has remained unchanged into urine.

Microbial evolutionary degradation of xenobiotics makes them able to acquire genetic mutation and traits to survive fighting against toxins utilizing them as sources of sulfur, phosphorus nitrogen and carbon. These microbes are thus utilized for the bioremediation of contaminants at a large scale. XRs (Xenobiotic Receptors) have a central role in controlling the expression of detoxification genes required for clearance and detoxification of xenobiotics. Highly toxic xenobiotics include mainly the NOCs (N-nitrosO-Compounds), the PAHs (Polycyclic Aromatic Hydrocarbons) and the HCAs (Hetero-Cyclic Amines).[4] Many of these xenobiotics are highly noxious and poisonous to cells, tissues and organs, creating dangerous and deadly health problems.

Xenobiotic metabolism is chemical transformation in living tissues utilizing Drug Metabolizing Enzymes (DMEs), which ideally converts relatively lipophilic, lyophilic, hydrophobic substances into more readily excretable hydrophilic, lipophobic products. The metabolism and biotransformation of one xenobiotic substance into another substance frequently involves multiple modifications in the parent substance. These modifications can occur through a sequence of several reactions leading to one or more new substances. Each new substance (product) has distinct physical, chemical, pharmacological and toxicological characteristics. Thus, xenobiotic metabolism and biotransformation may result in modified toxicological features, converting an active substance into another inactive substance or into an another active substance; or converting an inactive substance into an another active substance or into an another inactive substance. All organs and tissues of human body are the sites of xenobiotic metabolism and biotransformation, but the liver is the principal site, because the liver cells are specially empowered as they are endowed with required enzymes and endoplasmic reticulum. Xenobiotic metabolism and biotransformation are essential defensive reactions that can be best started as soon as the xenobiotic exposure occurred through such portals as. skin, respiratory and alimentary tracts. Kidneys are also rich in xenobiotic enzymes and accordingly they can tackle and handle a bulk of xenobiotics though it is not a portal. Xenobiotic metabolizing enzymes are also found in foetal and adult adrenal glands, placenta, testis, ovary, fetal and embryonic liver, corpus luteum, aorta and lymphocytes, platelets, gonads etc. Thus, it is evident that almost every tissue has some activities against xenobiotic substances, but major enzyme systems are there principally in the liver. The xenobiotic metabolism and biotransformation in extrahepatic tissues has an important toxicological significance for those particular tissues. Approximately 30 different enzymes in liver catalyze reactions involved in xenobiotic metabolism and biotransformation. But this covers only a selected group of them. Phase I reactions (metabolism and bio-transformaion) are oxidation, reduction and hydrolysis. However, the most noteworthy pathway here is the monooxygenation function catalyzed by the cytochrome P450s (CYPs; P450s). The CYPs detoxify and/or bioactivate a vast number of xenobiotic substances and carry functionalization reactions that include N- and O-dealkylation, aliphatic and aromatic hydroxylation, N- and S-oxidation, and deamination. Phase II reactions (metabolism and bio-transformaion) are the conjugation reactions, getting conjugated with glucuronic acid, amino acids (glycine), mercapturic acid, glutathione, sulfate, acetate and methyl groups. Generally, detoxification of a substance involves phase I and phase II reactions. For example, oxidation followed by conjugation is the most frequent process in the metabolism and biotransformation of xenobiotics. Phase III biotransformation involves a more newly termed descriptor that addresses to active membrane transporters that function to shuttle drugs and other xenobiotics across the cellular membranes.[1,3-5]

Most of these xenobiotics are lyophilic, lipophilic and hydrophobic. Thus, they get widespread distribution in the body by diffusion through biological bi-layered phospholipid membranes. They get accumulated in hydrophobic components of cells and tissues. They are not being excreted unchanged in urine by kidneys and liver through urine and bile respectively. They thus can interfere with enzymatic activities of cells. The cellular enzymes can prevent the detrimental effects of xenobiotics by metabolizing and detoxifying them. Making them more hydrophilic through metabolism by cellular enzymes, they are being excreted and eliminated from the body. Just like wastes from normal catabolic pathways, they are being expelled in the urine, feces, and exhaled air. Xenobiotics which are rapidly eliminated may undergo limited phase I metabolism (reduction, oxidation, or hydrolysis reactions) that make the hydrophobic & lipophilic substances into more polar molecules, adding or exposing such a polar functional group as amino (-NH2) or hydroxyl (-OH), carboxyl (COO-) etc. The notorious health consequences from xenobiotics range from allergic skin reactions to major life-threatening consequences involving cardiovascular, neurological, renal, hematological and reproductive systems. Many of them are mutagenic, carcinogenic and teratogenic affecting humans from the fetal life to the elderly stage. No organ is immune to detrimental effects of xenobiotics. Now toxicology deals with the notorious and noxious adverse effects of xenobiotics in living beings.[1,3-5]

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ABM Moniruddin
Professor of Surgery