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TRANSIENT AND TARGET ANIMAL TISSUES IN BIOACCUMULATION OF XENOBIOTICS

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Abstract. Xenobiotics are more and more present in our environment and consequently in our tissues. This paper is a review of the tissue bioaccumulation of a lot of harmful substances take in from the environment, disturbing the homeostasis and the health state of the human body. Bioaccumulation induce structural and functional disturbances at different levels: population, organism, tissue/organ, cellular and molecular. It has been found that some food additives, endocrine disruptors and heavy metals accumulate in the human tissues, inducing structural and functional changes. The epithelial tissue is usually a transient structure or a barrier for the xenobiotics. Liver, splin, kidney, skin and ovaries/testes, as organs, and the fat, bone, nervous and muscle tissues, are target structures for xenobiotics that could be accumulated, being persistent in the animal body and even in the ecosystems

Key words: Xenobiotics, Bioaccumulation, Bioconcentration, Tissues, Bio-education.

Introduction

Xenobiotics are defined as extrinsic chemicals to which an organism is exposed (Croom, 2012), compounds foreign to a living organism (Maurice *et al*., 2013) or chemicals which are foreign to the biosphere (Fetzner, 2002). Sugimura *et al.,* 1991, showed that human are continously exposed to naturally occuring xenobiotics (from food, for example cooked meat and fish in microwave ovens, food additives, endocrine disruptors, drinking water, tobacoo and burning wood smoke, alcoholic beverages, soda drinks, cofee, thea, drugs, antibiotics, cosmetics, etc.) and more and more numerous kinds of industrial and agricultural compounds (nanoparticles, pesticides etc.) in our daily lives. Some of them are involved in cancer development, so that the exposure to any mutagenic and carcinogenetic xenobiotics should be kept at minimum.

Markert, 2007, showed that the bioaccummulation is the process by which an organism acumulate one or more elements and/or compounds from it environment, in function of the bioavailability of the xenobiotics in combination

with species-dependant uptake and elimination processes. Bioaccumulation occurs within an organism, where a concentration of a substance builds up in the tissues and is absorbed (by food ingestion, by inhalation from air and by direct contact) faster than it is removed (Van der Hoop, 2012). According to Tonnelier *et al*., 2012, bioaccumulation refers to the continuous increase in the concentration of a chemical in an organism, compared to the chemical's concentration in the environment to which the organism is exposed (air, water, soil, food, etc.). Bioconcentration refers to an aquatic bioaccumulation.

Xenobiotics entering naturally in the vertebrate body use three main ways: lungs by inhalation, digestive tract by oral consumption and skin or other external mucous membranes as cornea or conjunctiva, by transdermal absorption (Yogesh *et al*., 2015). In histological terms, the xenobiotics may acrros three natural barriers, adapted to preserve the body homeostasis: the alveolocapillary membrane, the mucosa and submucosa layers of the digestive tract and the skin.

These barriers between external and internal environment consist mainly into an epithelium, similar with an „ecotone" zone in ecology, that could be simple or stratified, non-keratinized or keratinized, related to a wet or a dry external environment. There are also a lot of internal barriers, as the blood brain-barrier and the blood-testis barrier, that could be across by the different types of xenobiotics, mainly by nanoparticles.

For example, silver nanoparticles, that could be classified as a xenobiotic in the human body (Lansdown, 2010), have a potential antimicrobial activity (Panyala *et al*., 2008) against many pathogenic microbes. Silver nanoparticles are toxic to bacteria, viruses, fungi and yeast, but they are also toxic to mammalian cells, by binding to their proteins and enzymes, damaging brain, liver and stem cells. Silver can enter the human body by ingestion of contaminated diet and drinking water, even from dental amalgams, inhalation of particles in the air, or skin contact with textiles, cosmetics, jewellery, burn creams or wound care products and acupuncture needles.

Different chemical forms of silver are present around the body by the blood stream, but the target organs for bioaccumulation are the liver, kidney, spleen, brain, leptomeninges and choroid plexus, hart, skin, cornea, gingival and other mucous membranes, and nails.

According to Jakimska *et al.,* 2011, heavy metals are a group of environmental contaminants, strongly toxic and ecotoxic. Some of them, as Mn, Mo, Fe, Co, Cu and Zn are essential for organisms, becoming toxic only at high concentration. Some heavy metals, not known to play any metabolic function, such as Pb, Hg As and Cd are toxic even at low concentrations, being associated to many adverse effects on health.

Annabi *et al*., 2013, showed that fish have ability to assimilate, stored and accumulate heavy metals in their tissues, by the absorption along different epithelia: epidermis, gills and digestive tract.

The endocrine disruptors, usually present in plastics (including baby bottles, water and food containers and toys), cosmetics (sunblocks, shampoos etc.), pesticides, different air freshener fragrances formulas are hormonally active molecular compounds in the environment, altering the gene expression during early development, with a significant impact on the human health and wildlife populations (Gilbert and Epel, 2009). The endocrine disruptors may act as agonists – mimetic for a naturally hormone, antagonist – prevent the binding of a hormone to its natural receptor, they could increase the hormone synthesis, can affect the transport or elimination of a hormone from body and could increase the reaction of target cells to hormones. For example, the bioaccumulation of DDT in the fish induced in some pray birds that fed on fragile eggshells, resulting in high mortality.

Role of the epithelial tissues in bioaccumulation.

For example, the diffusion coefficient through the death stratum corneum located in the upper part of epidermis of terrestrial vertebrates, for any given compund, is consistently lower and a xenobiotic cannot easily pass through it. Invertebrates have an integument including a single layer epithelium, but there are a lot of epidermic productions, as cuticle, covering the body surface and largely decreasing the penetration area and rate of xenobiotics into the body, due to it chemical composition. The rate and intensity of penetration through the integument depends upon a large number of biological (types, structure and chemical compositions of skin appendages, particular types of cells involving in osmoregulation in aquatic animals as chloride cells and different types of sensilla functioning as chemosensors, the great area and the biochemical proprieties of epidermis, the skin metabolism, the degree of skin hydration, age, sex etc.) and environmental variables (concentration of xenobiotics, media-water, soil or air, temperature etc.).

The contribution of the dermal absorption of xenobiotics is considerable, the dermal route accounting for more than half as much uptake of chlorine from inhalation during a normal shower in chlorinated water (Poet, 2000). The dermal route may contribute significantly to the total body burden. The transdermal penetration consists on a suite of sequences as: adsorption of a penetrant molecule onto the surface layers of the epidermis, diffusion through the stratum corneum and through the malpighian part of the epidermis in terrestrial vertebrates and diffusion through the papillary dermis into the microcirculation (Peptu *et al*., 2015).

Usually, the skin is a transient organ of bioaccumulation. Nanoparticles, ultrafine and fine particles also, could penetrate the skin barrier. Particles of 500-

1000 nm in size can penetrate and reach the deeper levels of human skin (Yogesh *et al*., 2015). Micrometer-sized particles of TiO_2, used in sunscreens to absorb UV light, penetrate through the stratum corneum of the skin and into hair follicles, until the profound part of the skin. There are many nanoparticles that could reach the capillaries of the dermis, entering into systemic circulation, by which they could rapid pass the blood-brain-barrier, reaching the nervous tissues from the main organs of the central nervous system.

Nanoparticles can establish interactions with different epithelia (epidermis, alveolar epithelia, and intestinal epithelia) and can easily translocate, becoming distributed throughout the animal body. Absorption of silver in the skin is mentioned, but percutaneous absorbtion of silver ions through intact or damaged skin is low (Lansdown, 2010). Silver enhance the melanin production, leading to discoloration of the skin (Panyala *et al*., 2008) and can be deposited in nails or around other appendages of the skin. Small silver particles can enter the body through the sweet glands or the needles. In the generalized argyria, silver granules accumulate around the sweet eccrine glands, in the wall of blood vessels and along the dermal elastic fibers and basement membrane (Panyala *et al*., 2008).

10-20% of the ingested silver metal is absorbed in the gastrointestinal tract, especially in duodenum and small intestine. At the intestinal level, absorption of nanoparticles depends on their diffusion coefficient, accessibility through mucus, contact with enterocytes, cellular trafficking, and other subsequent absorption events. Small particles could faster permutate the mucus, while large 1000 nm particles are unable to translocate this barrier (Yogesh *et al*., 2015).

There are a lot of studies showing that the ultrafine and nanoparticles as diesel particles, carbon or TiO_2 administrated by inhalation produce more adverse effects as inflammation and tumors than the large chemical identical particles. Silver nanoparticles have higher pulmonary effects and show also a systemic distribution because they can enter through the cardiovascular system.

A main target organ for inhaled silver is the lung, where the nanoparticles are present immediately after the exposure. Some of inhaled particles, usually the larger sized, are eliminated by mucocilliary structures present in the respiratory tract; the fine particles, as nanoparticles, do not interfere with the mucocilliary elimination process, being phagocyted by the alveolar macrophages or bioaccumulating in the alveolar walls, occupying the alveolar space. Nanoparticles can be submersed into the surfactant lining the alveoli. During this process, nanoparticles produce surface radicals and reactive oxygen species that can induce the oxidative stress, damaging the lung epithelial cells.

The liver is the major organ primarily exposed to toxic and essential substances that enter the organism through inhalation or ingestion (Pereira *et al*., 2006). The liver sustained histological lesions and alterations, reacting to Cd concentration and time exposure. Cd is known to disrupt hepatic carbohydrate metabolism,

leading to a decrease in glycogen storage, increase plasma glucose and lipidosis (Annabi *et al*., 2013).

Fish gills also represent one of the main organism-water boundaries and the gill epithelium is the main entry surface for waterborne contaminants in fish. The gills are more susceptible to acquire histopathological lesions than the skin. They are considered "temporary target organ" of Cd accumulation. The highest Cd concentrations were observed in gills, but they are the most efficient organ detoxifying the metal. The Cd metal ion usually accumulated less in gills (Annabi *et al*., 2013).

Connective tissues in bioaccumulation.

The connective tissues are very diverse and complex, being involved in circulation and partition of the xenobiotics in animal body, like lymph and blood, or in effective bioaccumulation, being target tissues, like fat tissue, the dermis from skin or other membranes and also bone tissue. Macrophages, "scavenger cells" into the connective tissues, incorporate by phagocytosis different xenobiotics, such as nanomaterials.

Bisphenol A, other endocrine disruptors and different lipophilic xenobiotics accumulate in body fat, especially in hypodermis, that comprises almost 50% of the body fat, being gradually released over time (Tillet, 2009).

The chronic exposure to silver causes permanent argyria (blue-gray skin, due to the dermal deposition) and argyrosis (blue-gray eyes, due to deposition in the connective tissue of cornea and conjunctiva as well as in the mucosa of the abdominal viscera). The transdermal delivery of silver nanoparticles depends on damage of the epidermis. Silver accumulates in dermis and in the connective tissues of the mucous membranes (conjunctiva and gingival). Silver nanoparticles can cause inflammation. The higher concentration of silver nanoparticles are toxic to cells, interacting and disrupting the cell membrane, destroying the mitochondria, producing the toxic radicals and inducing the inflammation, apoptosis or necrosis of cells. Some gold nanoparticles induced the formation of actin filaments, resulting in a decrease in cell proliferation, adhesion and motility, even these nanoparticles skowed non-toxicity in skin cells (Fratoddi *et al*., 2015). For example, nanomaterials, like nanoparticles, arrived in the systemic circulation, where they are rapidly recognized and phagocyted by macrophages and by other cells of the reticuloendothelial system. Macrophages populated some target organs in bioaccumulation, as liver and spleen, very quickly, even in few minutes (Fedeel *et al.,* 2012).

Cheng et al., 2012, showed that the tetracycline is a fluorescent marker that accumulates in the bone tissue, being used to label new bone formation. The most study have shown that tetracycline is a strongly inhibitor on osteoclasts and osteoblasts, affecting the bone histomorphometry. Bassett *et al*., 1980, discovered that even the arcaeological ancient bones exhibit a yellow-green fluorescence

identicat to that of modern tetracycline-labeled bone. This bioaccumulation of tetracycline in the ancient bone is due to a Streptomycetes contamination by stored grains or beer. Also, 90% of the total body burden of Pb is found in bone tissue of small mammals (Preira *et al*., 2006).

Muscle tissue in bioaccumulation.

The bioaccumulated total lead (Sia Su *et al.,* 2013) and mercury (the most bioaccumulated and biomagnified metal in the muscles) (Kaoud and El-Dahshan, 2010) induce histological alterations in muscle: disintegration in the muscle fibers, spaces in between muscle bundles, and degeneration of the muscle bundles.

Bioaccumulation at the nervous tissue level.

Silver, under different forms, can enter into nervous tissue of the organs from the central nervous system, causing neurotoxic damage. The silver nanoparticles can cross the blood-brain barrier (Hritcu *et al.,* 2011) and also the small gold nanoparticles (Stefan *et al*., 2013), but the localization of xenobiotics is heterogenous in the central nervous system. It can accumulate in large motoneurons in the brain and spinal cord, in neurons of cerebellar nuclei and glia (Panyala *et al*., 2008). The biological half-life of silver in central nervous system is longer than in other organs. The safety of most of the nanomaterials used now in medicine, cosmetics or food has not been well assessed concerning their effects on the human body and environmental health. For example, silica nanoparticles below 100 nm diameter can penetrate the skin and showed a distribution into the nervous tissue of brain, into a different manner that the common large size materials, considered as safe, which can not be absorbed by the animal body (Tsunoda, 2011).

Bioaccumulation and the reproductive system.

Silver nanoparticles showed severe toxic effects on the male reproductive system. The nanoparticles cross the blood-testes barrier and are deposited in the testes, with a potential adverse effects on sperm cells (Panyala *et al*., 2008). Juvenile alligator males, affected by endocrine disruptors, have poorly organized seminiferous tubules, a reduced penis size, and testes have elevated estrogen production correlated with a decreasing in testosterone (Gilbert and Epel, 2009). Females have polyovular follicles due to an estrogenic excess.

Cadmium accumulates in the gonadal tissues of fish becoming harmful for reproduction. Fish sperm may be exposed to Cd through bioaccumulation in testis (Annabi *et al*., 2013).

Harris *et al*., 2011, showed that the endocrine-disrupting chemicals are estrogenic and antiandrogenic compounds present in almost all treated sewage effluents and in lowland rivers. Steroid estrogens are active at low concentrations and cause sex ratio alteration and feminization of male fish.

Conclusions

According to Goleman, 2009, and Brouwer, 2007, the xenobiotics have a huge ecological impact on our life, inducing a disturbance of our health and of the environment. Xenobiotics are present in our food, drinks, inhaled air, clothes, toys, drugs, but they cross the body barriers and migrate from outside into our internal environment, persisting also in our tissues, where they can induce structural and functional disturbances at different levels. By bioaccumulation and biomagnification, animals, including human, become more polluted than the external environment. This process determines a profound analysis based on the "ecological intelligence", driving to the implementation of the "bio-education" concept in our lifelong educational system.

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