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An Overview on Toxicity of Tributyltin

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Abstract

Tributyltin (TBT) is a highly toxic biocide that has been used extensively to prevent the growth of marine organisms on the hulls of large ships. It is a problem in the aquatic environment because it is extremely toxic to non-target organisms, is linked to immuno-suppression and imposex (development of male characteristics in females) in snails and bivalves, and can be persistent. Tributyltin (TBT) compounds include: tributyltin oxide, tributyltin benzoate; tributyltin chloride, tributyltin fluoride, tributyltin linoleate, tributyltin methacrylate, tributyltin naphthenate. Toxicity of organotin compounds is strongly influenced by the length of the alkyl chains attached to the tin. Tributyltin (TBT) is generally less toxic than trimethyl- and triethyltins. Tributyltin compounds are moderately toxic via both ingestion and dermal absorption. The tributyltin compounds may be strongly irritating to the skin in humans, especially the hair follicles, and skin exposure may result in chemical burns in only a few minutes if the concentration of tributyltin is high enough. Shipyard workers exposed to TBT (occupationally exposed to dusts and vapors) developed irritated skin, dizziness, difficulty breathing, and flu-like symptoms. Other mucous membranes such as the eyes and nasal passages may also become irritated upon exposure.

Keywords: Tributyltin, Toxicity, TBT.

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1. Introduction

Tributyltin (TBT) is an organotin compound. Organotin compounds (OTs) are synthetic organometallic chemicals which have been known since 1853. They did not become important for industrial use until the 1940s. Since then, they have come into extensive use in several industrial sectors with several commercial applications e.g. agricultural pesticides, wood preservatives, and antifouling paints on ships [1]. Tributyltin compounds are organic derivatives of tin (sn). They are characterized by the presence of covalent bonds between three carbon atoms and a tin atom. They conform to the following general formula (n-C4H9)3Sn-X, where X is an anion or a group linked covalently through a hetero atom (chloride, acetate, hydroxide, carboxylate and fluoride). The nature of X influences the physiochemical properties, notably the relative solubility in water and nonpolar solvent. Tributyltin chloride (TBTCL) is a colorless liquid with molecular formula (C12H27CLSn+) [2]. Tin usually binds to non-polar radicals resulting in hydrophobic compounds; and due to their physicochemical properties, OTs are easily absorbed along the food chain. The effects depend greatly on the number and nature of radicals bound to the tin atom, being the tri-substituted (triorganostannic) forms, such as tributyltin the most toxic.

TBT is degraded in the environment to dibutyltin and then to monobutyltin. In the aquatic environment, TBT is quickly removed from the water column and adheres to bed sediments because TBT has a high specific gravity near 1.2 kg at 20 °C , low solubility less than 10 mg at 20 °C and pH7.0 , and log Kow values near 4.4 at pH 8 [3]. Additionally, TBT is ionisable and exhibits a pKa acidity constant of 6.25. TBT sorption/desorption with natural sediment can be strongly influenced by changes in the pH and salinity**.** Increased artificial seawater salinity generally reduced TBT sorption at pH 4 and 6, but enhanced TBT sorption at pH 8. Regardless of salinity, maximum sorption of TBT was observed at pH 6, which is attributed to an optimal balance between the abundance of cationic TBT+ species and deprotonated surface ligands. Tributyltin compounds have ahigh fat solubility and tend to absorb more readily to organic matter in soils or sediment [4]. The TBT toxicity has become a major concern for the scientific community since the 1970s when toxic effects were discovered in different animal models, including mammals. These compounds can be easily assimilated by living organisms; in marine environment, for example, OTs are incorporated into soil and organic surface sediments such as phytoplankton, being absorbed by animals and plants of aquatic ecosystems. Studies have shown that OTs cause several damages, including genetic, hepatic, renal, adrenal, neural, and immune toxicity [5].

1.1. Endocrine disrupting effects

Endocrine disruptors (EDs) are chemical substances widely used in industry, distributed in the environment and able to interfere with the synthesis, release, transport, metabolism, receptor binding, action, or elimination of

endogenous hormones [6]. Organotins can directly damage endocrine glands, as well as interfere with neurohormonal control of endocrine function (i.e., in the hypothalamic–pituitary axis), altering hormone synthesis and/or bioavailability or activity of hormone receptors in the target cells. In addition, the endocrine dysfunction due to OTs exposure can be mediated also by general toxic effects, such as increased oxidative stress and damages to mitochondrial function and subsequent responses to cellular stress. The inhibition of ATP synthesis evidenced by studies with OTs exposure could thereby trigger similar biochemical and/or endocrine dysfunctions [7]. Reports indicate that TBT is a highly persistent chemical in the environment and food chain, being considered one of the largest existing endocrine disruptor with consequences to different hormonal functions. Tributyltin is also able to disrupt the normal function of the pancrease, pituitary gland, gonad (male and female), bone, mineral metabolism, thyroid and breast, this disruption could contribute to the development of endocrine and metabolic disorders such as insulin resistance and obesity [8].

1.2. Reproductive effects

The hypothalamic-pituitary-gonadal (HPG) axis is the principal modulator of reproductive function. In females, the hypothalamic gonadotropin-releasing hormone (GnRH) neurons play a pivotal role in the regulation of the cascade of hormonal events necessary for normal reproduction**.** GnRH is a peptide synthesized and released by GnRH neurons that stimulates the production and secretion of luteinising hormone (LH) and follicle stimulating hormone (FSH) in gonadotrophs**.** LH and FSH act on their respective receptors to stimulate ovary maturation and estrogen production. Estrogens are steroid hormones synthesized in females within the ovarian granulosa cells, and many of their actions are mediated by nuclear estrogen receptors (ERs). The ERs are composed of ER alpha (ERα) and ER beta (ERβ)**.** ERα expression is predominately present in the hypothalamus, pituitary and uterus**.** ERβ expression is mainly present in the hypothalamus, ovary and lung**.** In the female brain, estrogen plays a critical role in the regulation of GnRH neuron activity and gonadotrophs, with bimodal effects on the hypothalamus, including inhibitory and stimulatory influences on GnRH secretion (estrogen negative and positive-feedback) [9].

TBT impaired the metabolic control in the hypothalamic pituitary-gonadal axis and ovarian steroidogenesis and increased adrenal lipid accumulation in adult female rats due to immune and oxidative stress responses**.** Studies have supported the key roles of inflammatory mediators, obesity and leptin in abnormal HPG axis function**.** Increased oxidative stress (OS) is associated with reproductive tract abnormalities in female rats [10], Leptin belongs to a family of protein hormones that is synthesised and secreted in white adipocytes regulating feeding behavior, energy expenditure and regulating different physiological processes including reproduction**.** leptin action modulation of GnRH secretion is exerted via interneurons that converge on GnRH neurons, such as Kiss neurons**.** Kiss neurons are localised in the arcuate (ARC) and anteroventral periventricular (AVPV) nucleus in the rodent hypothalamus**.** The leptin receptor is expressed in the Kiss1 neurons of the ARC nucleus [11].

Kisspeptin (Kiss) is a neuropeptide that has shown to be powerful stimulators of GnRH synthesis and secretion in mammals**.** Previous studies have demonstrated the general concept that Kiss-secreting neurons expressed and activated GnRH neurons to advance process of reproductive axis control. The reproductive HPG axis abnormalities identified in TBT rats associated with an increase in the serum leptin levels as a result of obesity induced by TBT [12]. Merlo et al. [13] also have reported that TBT induced GnRH expression reduction related to an impaired Kisspeptin/leptin signaling. Tributyltin exposure alter hypothalamic pituitary-gonadal axis, adipocyte hypertrophy, hyperliptenemia, reduced gonadotrophin-releasing hormone expression, luteinizing hormone levels, irregular estrous cyclicity, improper ovarian folliculogenesis, reduced ovarian reserve and increased reproductive tract inflammation and fibrosis in female rodents**.** As well as reports showing uterine atrophy, presence of macrophages and neutrophils and greater caspase-3 mRNA expression resulting from TBT exposure in female rats [12].

1.3. Obesogenic effects

Obesogens are defined as chemicals (natural, pharmaceutical, or xenobiotic) that promote obesity by increasing the number of fat cells or the storage of fat in the existing fat cells**.** They can also indirectly act by changing the basal metabolic rate, by shifting energy balance to favor the storage of calories and by altering hormonal control of appetite and satiety**.** Tributyltin chloride is an obesogen associated with various metabolic and reproductive dysfunction after in utero exposure [14]. These endocrine and metabolic disorders caused by OTs, particularly obesity, may occur by central and peripheral mechanisms**.** In the central nervous system hypothalamus act as the control centre for hunger and satiety. Part of the hypothalamus, the arcuate nucleus includes neurons that co express peptide that stimulate food intake and weight gain, especially neuropeptide Y (NPY) and agouti related peptide (AGRP), as well as those expressing proopiomelanocortin (POMC), cocaine and amphetamine regulated transcript (CART) which inhibit feeding and promote weight loss. Together these neurons and peptides control the sensations of hunger and satiety and thereby regulae apetite and energy balance**.** Tributyltin induced brain NPY expression in the female rats which led to increase food intake and depressed brain POMC and CART expression in male rats.

Tributyltin induced astrocyte apoptosis in rockfish thus the depression of neuropeptide expression in male rats would be due to the cytotoxicity of TBT**.** Studies showing that NPY expressing neurons in the hypothalamus concentrate 17 Beta oestradiol and the sex steroid estrogen play arole in the regulation of NPY synthesis**.** Therefore TBT had sex-different effects on brain neuropeptide expression might be due to the neuro-protection of 17 Beta oestradiol in the brain where females have higher levels compared to males [15]. In relation to peripheral mechanisms involved in the obesogenic effect, it is well described the association between tin-based compounds and adipogenesis, through signaling between retinoid X receptor (RXR) and peroxisome proliferator-activator receptor gamma (PPARγ)**.** There are evidences that TBT increases adipocyte markers expression, lipid accumulation and glucose uptake in preadipocytes and induces a differentiation to adipocytes by RXR/PPARγ activation. Prenatal exposure to environmental TBT predispodes multipotent stem cells to become adipocytes in mice**.** Tributyltin chloride (TBTc) induces adipogenesis, interfere with energy homeostasis and affect hormons involved

in mammalian body weight regulation by attenuating the transport of leptin to the hypothalamus, via blood-brain barrier, therefore producing a condition of obesity [14].

1.4. Fetal effects

Tributyltin exposure during gestation is very critical as the placenta and fetal tissues are absorbing TBT from maternal circulation and accumulating within their tissues, inducing toxic effects such as abnormal fetal development, an imbalance in the hypothalamic pituitary- gonadal axis, alteration in sexual hormones, the role of sexual enzymes and decreases in the weights of sex organs [16]. Tributyltin exposure during early pregnancy produce adverse pregnancy outcomes as developmental disorder of placenta via dysregulatipon of key molecules, proliferation, apoptosis and oxidative stress, as well as TBT exposure led to implantation failure, decreased uterine weight, serum progesterone levels, also dramatically increased the incidence of low birth weight fetuses and increase in the number of resorbed emberyo. Tributyltin treatment during early pregnancy Studies in female rats showed that in utero exposure to (TBTC) (at 20 mg/kg) leads to a decrease in maternal weight gain and fetal weight, induces pre- and post-implantation losses, increased in pregnancy failure by 84.6% after 16.3 mg/kg, increases rat fetal toxicity after 25 mg/kg of TBTC treatment [17].

1.5. Immunotoxic effects

Tributyltin is proved to be immunotoxic. This immunotoxicity is associated with thymocyte apoptosis and that this process is mediated by the Fas pathway**.** Fas and Fas ligand (Fasl) are members of the tumer necrosis factor (TNF) -receptor and TNF family, respectively. The ligation of Fas with Fasl results in the activation of a caspase cascade that initiates apoptosis. Tributyltin chloride has been found to reduce the spleen and thymus weights, suppresses both the humoral and cellular immune responses, reduces peripheral lymphocytes, modulating cytokine release, such as Tumor necrosis factor (TNF) and Interferon -gamma (INF -γ). In addition, depletion of lymphocytes in the spleen and lymph nodes, and alteration of serum immunoglobulin levels [18].

1.6. Nephrotoxic effects

The kidneys are especially vulnerable to environmental contaminants because they are a metabolizing site of xenobiotics. Therefore, pollutants can accumulate in renal tissue, leading to impaired renal function and several renal abnormalities. Organotin exhibits the inhibitory action on the activities of enzymes H+/K+-ATPase and Na+/K+-ATPase, resulting in hypokalemia (increased K+ leakage) and acidosis (decreased H+ secretion). These imbalances lead to an increase in urinary pH and thus raise the risk of kidney stone formation. Tributyltin nephrotoxicity is due to the enzymatic and non-enzymatic antioxidant defense systems become deficient and there is a consequent uncontrolled generation of (ROS) that leads to lipid peroxidation, abnormal cellular function, renal tissue damage and cell death. [19].

1.7. Hepatotoxic effects

Subchronic exposure to low dose tributyltin resulted in multi-organ toxicity including the liver**.** Tributyltin mediated oxidative stress induces impairments and damage in the liver**.** Tributyltin exposure causes endoplasmic reticulum(ER) stress and unfolded protein response (UPR) activation to enhance the folding capacity of the ER and degrade unfolded protiens. When the exposure concentration increased the UPR could not restore the ER to its normal state, autophagy was triggered and the damaged organelles were engulfed by autophagosomes. When the TBT concentration continued to increase, autophagy could not eliminate the damage and finally sever damage initiated the process of apoptosis in liver cells [20].

1.8. Neurotoxic effects

Blood brain barrier integrity is vital in maintaining the micro-environment of brain tissue and its disruption is the initial event in several neurological diseases. TBT was found to interact with phospholipid bilayer of cell membrane which lead to transient increase in BBB permeability [21]. Fortier et al. [22] reported that TBT finds its access to the brain directly via sensory organs like the retina and axonal transport or indirectly after its metabolism. The highest levels of TBT are in the cerebral cortex and the lowest levels are in the cerebellum. Therefore cerebral cortex is representing the target area of structural alternation caused by TBT in brain. Organotin compounds induce generation of oxidative stress, astrocyte activation, overexpression of inflammatory molecules such as Interleukin-6 (IL-6), Cyclooxagenase-2 (Cox-2), and Nuclear factor kappa-B (NF-Kb) that lead to demyelination and edema. Also they induce neurodevelopmental abnormalities, loss of vigilance, disorientation and memory deficits. Tributyltin exposure has altered the redox homeostasis, diminishes zinc content in cortical tissues which reduces the brain's antioxidant capacity**.** The endocrine disruption caused by TBT leads to reduced levels of estrogens by the competitive inhibition of aromatase**.** As the antioxidant role of estrogens in the central nervous system has been reported, it is possible to assume that TBT also influences the ROS generation in the brain by suppressing the circulating levels of ovarian estrogen. It was also reported to induce dysregulation of caspase-3 expression, Bax, and Bcl-2 as indicative of the apoptotic mechanism mediated by TBT in brain tissue [23].

1.9. Respiratory toxic effects

Organotin exposure leads to respiratory toxicity by inflammation. OTs' contact could elevate airway inflammatory response, throughout a mechanism associated with apoptosis of T-regulatory cells and increased oxidative stress response. In addition, OTs induce macrophage recruitment to tissue, leading to increased necrosis, which stimulates an inflammatory cytokines secretion exacerbating local inflammation and tissue function loss [24].

1.10. Cardiovascular toxic effects

Studies have showed that TBT exposure causes abnormal vascular reactivity such as increased oxidative stress, disbalance in nitric oxide (NO) bioavilability, abnormal endothelium function, vascular remodling and decreasing of estrogen levels that can significally change the vascular response**.** Tributyltin is reported impair the coronary vascular reactivity to estradiol, as well as, altering aorta morphology and functionality**.** Tributyltin induced a negative inotropic effect in acute exposure. Moreover, it increased cytosolic and mitochondrial ROS production in cardiac myocytes. TBT induced cardiac dysfunction was also related to a dysfunction in calcium handling by cardiomyocyte [25].

1.11. Pancreatic toxic effects

Tributyltin is capable of inducing pancreatic β-cell apoptosis and dysfunction through activating the c-Jun N-terminal kinase (JNK) pathway. Moreover, ROS acts as an upstream key signaling molecule in TBT-induced JNK activation [26].

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